BMC Infectious Diseases

RESEARCH

Open Access

Tuberculosis mortality and drug resistance among patients under TB treatment before and during COVID-19 in Burundi: a case–control study

Arnaud Iradukunda[1,2*], Fentabil Getnet[3] and Emmanuel Nene Odjidja[4]

Abstract

Background The coronavirus SARS-CoV-2 (COVID-19) experience has underscored the consequences of inequalities in health and access to health services across and within countries. Vulnerable population groups have been disproportionately exposed to certain diseases such as tuberculosis (TB) due to service interruptions. The current study aimed to assess TB related mortality and risk of drug resistance during the COVID-19 Pandemic in Burundi.

Methods We conducted an incident case–control study on 362 TB patients, with 181 multidrug resistant TB (MDR-TB) patients and 181 drug susceptible TB (DS-TB) patients. These patients under TB treatment between July 11, 2018, and November 11,2022 (18 months before and 18 months during COVID-19). Baseline and drug susceptibility status data were captured at treatment initiation. Mortality during treatment follow-up TB mortality was compared between categories of drug susceptibility, period (before vs during COVID-19) and regimen phase. A multivariate logistic regression was used to show the predictive risk factors. K-Fold cross-validation was used to evaluate the final model.

Results A half of TB patients was under 40 years old, with majority of them being unemployed, malnourished and lacking food support during TB treatment. Most of them lived in precarious conditions with limited access to healthcare services. The overall TB-related mortality was 16.0% (95% CI: 12.5%- 20.3%) with 15.5% (95%CI: 10.7%-21.8%) in MDR-TB patients and 16.6% (95% CI: 11.6%-22.9%) in DS-TB patients. Stratified by the period, TB related mortality was 15.3% (95%CI: 11.7%-20.9%) before the COVID-19 pandemic and 17.1% (95%C 11.5%-24.6%) during the COVID-19 pandemic. More than a half of deaths in TB patients occurred during intensive phase of treatment. The risk of MDR-TB was significantly higher ($p < 0.05$) among patients undergoing treatment during the pandemic, those with a low education level, living in rural areas, unemployed, using public transportation, or living in overcrowded households (big family size,a small number of rooms). Additionally, patients with history of TB, previous treatment failure, and close contact with MDR-TB patients were more likely to have MDR-TB. The likelihood of MDR-TB further increased with the cumulative presence of these risk factors on the same TB patient.

Conclusion TB mortality increased during the COVID-19 pandemic, particularly among MDR-TB patients. The odds of MDR-TB encompass a range of socio demographic and clinical factors particularly among economically disadvantaged patients. These findings underscore the need for targeted equity-driven interventions in high-risked

*Correspondence:
Arnaud Iradukunda
arnaudiradukunda5@gmail.com
Full list of author information is available at the end of the article

populations, especially in the context of emerging outbreaks, in order accelerate TB elimination goals. Additional investigation on TB related mortality should focus on the intensive phase of treatment, which aligns with the 2025 World Health Organization consolidated guidelines on TB diagnosis and control.

Keywords Tuberculosis, Multidrug resistance, Risk factors, Mortality, Covid-19, Burundi

Evidence before the study

Research context

Several key factors characterized Tuberculosis (TB) -related mortality and multidrug-resistant TB (MDR-TB) risk during the COVID-19 pandemic. Burundi as many low-income countries (LICs) has been grappling with a high burden of TB infection for years. The incidence of MDR-TB, where TB bacteria become resistant to at least Isoniazid and Rifampicin drugs, has been a growing public health concern.

TB control efforts have never been sufficient to address the existing TB burden effectively. Prior studies conducted in the sub-Saharan region highlighted gaps in TB control programs, healthcare seeking and treatment adherence issues, challenges in diagnosing drug-resistant TB, and the need for improved healthcare infrastructure and resources. The emergence of the COVID-19 pandemic caused multifaceted social and economic challenges including health and health services. The impact of the pandemic would be more significant in TB where Immune response to COVID-19 would trigger reactivation of latent TB and interruptions of TB control services would affect directly observed treatment-short course (DOTS).

By comparing TB data before and during the COVID-19 pandemic, the study will shed light on how COVID-19 might have affected TB burden in affected communities particularly on increased risks of TB related mortality and drug resistance. This insight is crucial for understanding the broader impact of the pandemic on major public health problems such as TB and MDR-TB. This study intended to investigate the changes in TB mortality and MDR-TB risk patterns attributable to disruptions in essential healthcare services, challenges in accessing treatment. This analysis will provide valuable information on TB related mortality and key factors influencing MDR-TB in Burundi, important for supporting the 2025 WHO consolidated guidelines on critical components of TB diagnosis and control.

Background

Tuberculosis (TB) remains a major public health concern in the World [1]. In 2023, TB likely regained its position as the leading cause of death from a single infectious agent worldwide, after being surpassed by COVID-19 for three consecutive years [2]. TB caused 10.6 million new illnesses and 16% case fatality rate in 2022 globally, the highest figure since World Health organization (WHO) commenced global TB monitoring in 1995 [3, 4]. This made TB as the world's leading cause of mortality from a single infectious agent only next to the coronavirus disease (COVID-19) [5]. More than 80% of TB caseloads occurred in Low and Middle Income Countries (LMICs) [6] in which Southeast Asia and Africa contributed to 44% and 24% of the global TB burden, respectively [4].

COVID-19 pandemic has exacerbated the pre-existing challenges associated with TB, particularly in vulnerable population groups, by increasing transmissions, disruptions in TB services and altered pathophysiologic conditions [7]. Based on the immunological mechanisms involved, COVID-19 and TB have a shared immune response dysregulation [8, 9]; both attack primarily the lungs and interfere with host immunity, and transmit mainly via aerosols and droplets from infectious patients [10]. Co-infection presents a dual risk as it worsens COVID-19 severity and facilitate TB disease progression [8], increasing vulnerability in co-infected patients [8, 11]. Furthermore, COVID-19 pandemic increased health inequities and disparities in in access to health services [12–14]. The economic decline and associated factors, such as income instability, food insecurity, and housing challenges post-pandemic, have created conditions that facilitate the spread of TB, which was yet a leading cause of mortality in resource-limited settings [15]. The COVID-19 impact was expected to increase extreme poverty, driving an additional 20 million people into extreme poverty [16, 17].

Efforts to end the TB epidemic have faced multiple challenges [18]. High rates of undetected and untreated TB cases [19], and rising of multi-drug resistant tuberculosis (MDR-TB) [20], and the recent lack of pandemic preparedness held back years of progress towards WHO's targets [21–24]. Burundi delayed to introduce global public health measures and vaccine in the national COVID-19 response plans [25]. Early in the pandemic, measures such as 14-day quarantine for incoming travelers were introduced in 2019, but broader public restrictions, including limits on gatherings, were not implemented [26, 27]. During most of 2021, Burundi delayed COVID-19 vaccine distribution, prioritizing prevention over vaccination, citing high recovery rates. Mass vaccination

only began in October 2021 with the arrival of 500,000 Sinopharm doses from China [28].

The limited public health response during the COVID-19 pandemic has significantly disrupted TB services, adversely affecting treatment outcomes and potentially accelerating, TB diagnosis and treatment delay, latent TB reactivation and the emergence of drug resistance [16, 29]. Prior to the pandemic, retrospective studies using routine TB surveillance data in Kenya had already demonstrated an elevated risk of mortality within the first two months of treatment initiation [30–32].Similarly, additional findings highlighted increased mortality during the intensive treatment phase among patients with multidrug-resistant TB (MDR-TB) [33]. The most recent WHO Global TB Report corroborates these findings, documenting early treatment-phase mortality in several high TB-burden countries [34].

To support the national efforts to End TB by 2035 and to better mitigate future pandemics, it is essential to assess the impact of COVID-19 on TB and MDR-TB. To best of our knowledge, the extent to which COVID-19 affected the TB program in Burundi, particularly TB related mortality and MDR-TB risk, was not well understood and documented. Moreover, it is also useful to investigate other underlying drivers of TB mortality and MDR-TB to inform the provision TB treatment services [35].Therefore, the current study aimed to assess TB related mortality and multidrug resistance rates during the COVID-19 pandemic in comparison with pre-COVID-19 period in Burundi. Other risk factors of MDR-TB and their interactions were also examined.

Methods and materials

Study settings

A total of 308 health facilities provides TB treatment in Burundi according to the national guideline and 170 of them provide smear microscopy services. This study was conducted at *Centre Anti-Tuberculeux de Bujumbura* (the main centre for the treatment of DS-TB) and *Kibumbu Sanatorium* which is the sole centre for treatment of MDR-TB in the country [36]. Kimbumbu Sanatorium national reference laboratory is a centre for culture and TB drug susceptibility testing services. The two centres were chosen based on their geographic representation (urban, rural) and their specialization in TB management in Burundi.

Study design and population

This was an incident case–control study conducted between June 11, 2018 and November 11, 2022, which was split into 18 months before COVID-19 and 18 months during COVID-19 at the COVID-19 pandemic declaration on March 11, 2020 [37]. Cases were bacteriologically confirmed MDR-TB patients diagnosed at CATB and referred to Kibumbu for MDR-TB treatment during the study period. Gene-Xpert MTB/RIF tests are used to bacteriologically confirm MDR-TB, and since isoniazid resistance test was not available in Burundi, all rifampicin-resistant patients were considered as MDR-TB patients and treated with second-line drugs for MDR-TB. Controls were bacteriologically confirmed and drug susceptible TB (DS-TB) patients who were on the first-line TB treatment at CATB during the study period. Patients treated during the COVID-19 pandemic (March 11, 2020, to November 11, 2022) were considered as exposed to COVID-19 and its consequences while TB patients treated during the pre-pandemic period (July 11, 2018, to March 11, 2020) were considered as non-exposed to COVID-19.

All pulmonary TB patients aged 15-years-old and above and who attended and followed at CATB during the study period were included and recruited into cases. Controls selection was based on drug resistance status. However, patients with TB involving meninges or bones and joints were excluded from the study since it takes 12 months to treat such forms of TB. Furthermore, patients admitted to TB treatment before COVID-19 and continued to be on treatment during the COVID-19 Pandemic period were excluded from the study as this might blur the comparison between the two periods. All patients included were selected at CATB.

Controls were selected using a risk set sampling method. With the risk set sampling, the odds ratio provides a good risk ratio regardless of the frequency of outcome because the controls provide an accurate estimate of the distribution in source population. The minimal sample size of 181 cases was calculated with a ratio of one case to one control [38]. Therefore, a total of 362 patients (181 cases and 181 controls) were included in the study.

Data collection

Data were retrieved from medical records using a form prepared for this purpose based on the review of literature and TB recording formats in Burundi. Systematic studies have shown wide variability of risk factors for TB related death across settings as well as different methodological approaches to assess risk factors have been used [39]. At TB treatment centers, baseline data are captured and thereafter, patients are followed up during routine clinic visits for controls or hospitalization for cases during treatment period in Burundi. Data on patients under TB treatment between June 11, 2018, and November 11, 2022, was collected from January 23,2023 to May 2023. We extracted data on socio-demographic and clinical characteristics; TB diagnosis, treatment and follow-up; treatment outcomes, and comorbid conditions. Additional information on routine follow-up of MDR-TB patients related to their status during 2 two first months

of treatment and treatment outcomes at the end of routine follow-up were collected.

Measurement

Multidrug resistance

As the isoniazid resistance test is not available in Burundi, all rifampicin-resistant patients were considered MDR-TB patients. Patients were labelled as 'Yes' if resistant to rifampicin and 'No' otherwise.

Mortality

Since there was cause of death assignment, all deaths of TB patients while on treatment for TB were considered as TB related mortality. Death was labelled as 'Yes' if a TB patient died during TB treatment period and 'No' otherwise.

Period

The official COVID-19 declaration by WHO as pandemic was set as reference [40]. The pre-COVID-19 was 18 months before the declaration. The COVID-19 period was 18 months after declaration.

Statistical analysis

Descriptive analyses were done to summarize TB related mortality and other explanatory variables. To compare proportions of TB related mortality, we used the Z-test. Both univariate and multivariate logistic regressions were used to identify factors associated with MDR-TB occurrence. The Wald test from univariate logistic regression and p-value cut-off point of 0.25 were used to determine the significance of independent variables on the MDR-TB [41, 42]. Univariate analysis do not capture the potential significant contribution of the combination weakly associated factors on the outcome [43].A high cut off of point ($p < 0.25$) was therefore used in order to adjust potential confounding effects [44]**.**We used the backward method and the Bayesian Information Criterion (BIC) to select variables for the final model. Odds ratio with their 95% confidence intervals (CI) were used to estimate the risk and statistical significance was determined at a low p-value($p < 0.005$). Multicollinearity between factors was assessed using the Generalised Variance Inflation Factor (GVIF) [45].

The relevance to make prediction of the final model was assessed using the Pearson residuals test. The Receiving Operating Characteristics (ROC) and Area Under Curve (AUC) were used to respectively evaluate the discriminatory performance and predictive power of the model [46, 47]. Thus, the AUC was calculated to validate the performance of the model using a bootstrapping procedure with 2000 replications. We finally used the machine

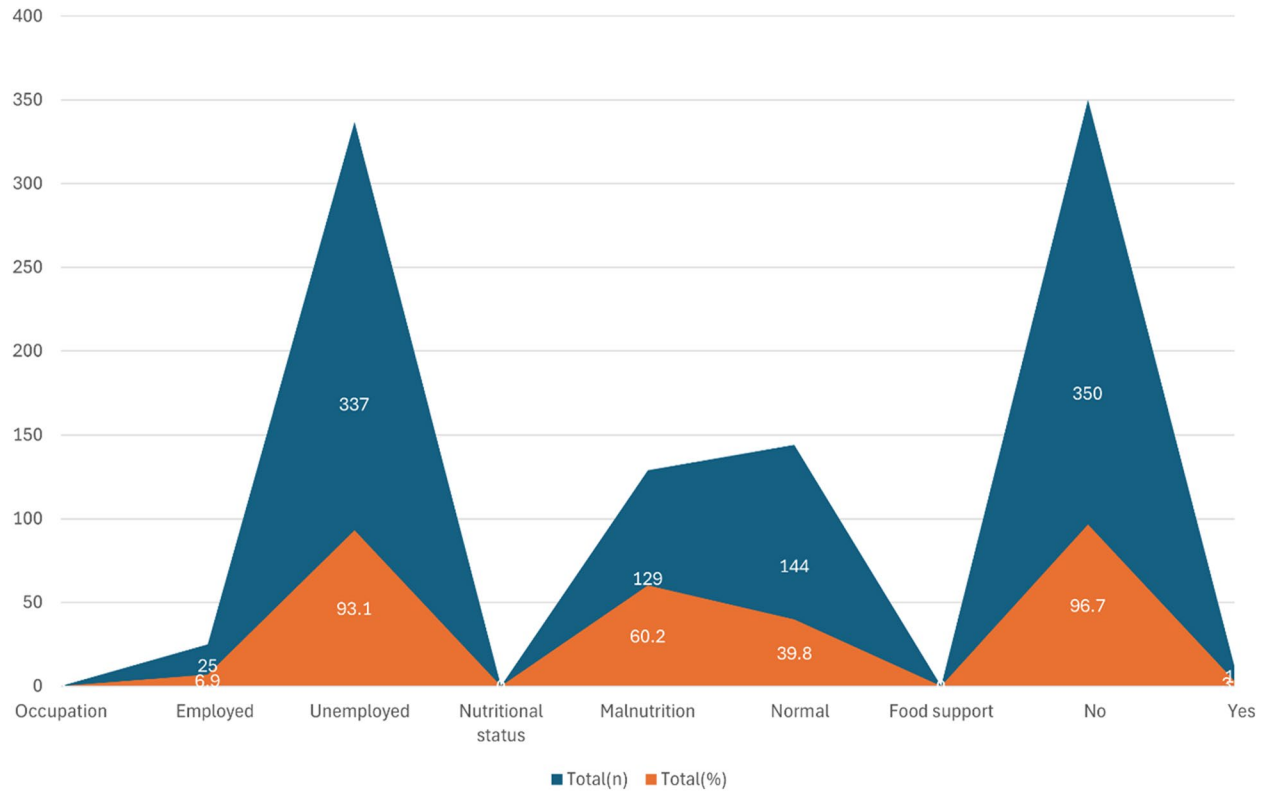

Fig. 1 Profile of TB patients

Table 1 Socio-demographic characteristics of DS-TB and MDR-TB patients in Burundi between July 2018 and November 2022

Characteristics	**Number**	**Percentage**	**DS-TB($n=181$)**		**MDR-TB($n=181$)**	
Socio-demographics conditions	***N*= 362**	**%**	***N***	**%**	***N***	**%**
Period						
Before COVID-19	222	61.3	122	67.4	100	55.2
During COVID-19	140	38.7	59	32.6	81	44.8
Sex						
Female	100	27.6	46	25.4	54	29.8
Male	262	72.4	135	74.6	127	70.2
Age (in years)	40 ± 14.9	[15–86]				
Pregnancy						
No	94	26.0	42	23.2	52	28.7
Yes	6	1.7	4	2.2	2	1.1
Occupation						
Employed	25	6.9	13	7.2	12	6.6
Unemployed	337	93.1	168	92.8	169	93.4
Marital Status						
Married	136	37.6	66	36.5	70	38.7
Not-married	226	62.4	115	63.5	111	61.3
Origin						
Burundian	359	99.2	178	98.3	181	100.0
DRC	3	0.83	3	1.7	0	0.0
Residence						
Rural	93	25.7	32	17.7	61	33.7
Urban	269	74.3	149	82.3	120	66.3
Living conditions						
Tobacco smoking						
No	282	77.9	162	89.5	120	66.3
Yes	80	22.1	19	10.5	61	33.7
Alcohol consumption						
No	286	79.0	162	89.5	124	68.5
Yes	76	21.0	19	10.5	57	31.5
Diabetes						
No	346	95.6	178	98.3	168	92.8
Yes	16	4.4	3	1.7	13	7.2
Nutritional status						
Moderate malnutrition	129	35.6	69	38.1	60	33.1
Normal	144	39.8	74	40.9	70	38.7
Severe malnutrition	89	24.6	38	21.0	51	28.2
Food support						
No	350	96.7	181	100.0	169	93.4
Yes	12	3.3	0	0	12	6.6
Prior incarceration						
No	343	94.8	177	97.8	166	91.7
Yes	19	5.3	4	2.2	15	8.3
Collective residence						
No	325	89.8	172	95.0	153	84.5
Yes	37	10.2	9	5.0	28	15.5
Household size						
≤ 6	273	75.4	158	87.3	115	63.5
> 6	89	24.6	23	12.7	66	36.5

Table 1 (continued)

Characteristics	Number	Percentage	DS-TB($n=181$)		MDR-TB($n=181$)	
Socio-demographics conditions	***N*** **= 362**	**%**	***N***	**%**	***N***	**%**
Person by room						
1	25	6.9	4	2.2	21	11.6
2	168	46.4	99	54.7	69	38.1
3	136	37.6	63	34.8	73	40.3
4	28	7.7	13	7.2	15	8.3
5	5	1.4	2	1.1	3	1.7
Distance home-HF						
< 3 km	232	64.1	108	59.7	124	68.5
3–10 km	3	0.8	0	0	3	1.7
> 10 km	51	14.1	21	11.6	30	16.6
Unestimated	76	21.0	52	28.7	24	13.3
Public transport						
No	180	49.7	102	56.4	78	43.1
Yes	182	50.3	79	43.6	103	56.9

learning approach, the K-Fold cross-validation method, to validate our prediction model [48, 49]. We used the C statistic to calibrate our model, which gives the probability that a randomly selected subject who experienced the outcome will have a higher predicted probability of having the outcome occur than a randomly selected subject who did not experience the outcome. Data analysis was done using R Studio 4.4.1 version.

Results

Sociodemographic and clinical characteristics

The median age of TB patient was 40 years old**.** Most of them were unemployed (93.1%). Malnutrition was observed in 60.2% of patients and 96.7% of patients didn't have food support (Fig. 1). Moreover, 62.7% were with less than three rooms in their household (Table 1). Reported TB cases were higher before COVID-19 compared to COVID-19 period. The figure below shows the profile of TB patients.

A third of MDR-TB cases occurred during COVID-19, and MDR-TB was observed among male patients (70.2%), unemployed patients (93.4%), patients using public transport (56.9%) and patients living in shared room (88.4%). Additionally, MDR-TB was present among patients with malnutrition (61.3%) and without food support (93.4%). The table below shows socio-demographic and living conditions of both TB patients.

Most of the TB patients, both MDR and DS TB, did not have hospitalization history (78.7%), TB history (79.0%), MDR-TB history (92.5%), history of treatment failure (89.2%), MDR-TB close contact (84.5%), clinical instability at the initiation of treatment (55.5%) (Table 2). More than a third of patients were HIV-TB coinfected. Most MDR-TB patients were TB patients with delays to TB diagnosis (88.9%). The table below shows the clinical conditions of patients.

TB related mortality

The overall TB related mortality was 16.0% (95% CI: 12.5%- 20.3%); 15.5% (CI:10.7%−21.8%) among MDR-TB patients and 16.6% (95% CI:11.6%−22.97%) among DS-TB patients. Of the total 58 deaths, 24 patients died during COVID-19 while 34 died before COVID-19. Nearly three-fourths of deaths (70.1%) occurred during the first two months of treatment (Table 2). More than a half (51.2%) of death among MDR-TB patients occurred also during the first two months of treatment. TB related mortality increased, not significantly, from 15.3% before COVID-19 to 17.1% during the COVID-19 pandemic. Before COVID-19, most of deaths (67.7%) were from DS-TB patients while during COVID-19 most of deaths (70.8%) occurred among MDR-TB patients (Fig. 2). The MDR-TB related mortality significantly increased during COVID-19 compared to pre-COVID-19 period ($p=0.001$). The figure below shows the TB related mortality between July 2018 and November 2022 in Burundi (Table 3).

Factors associated with multi-drug resistance tuberculosis

The table below shows the results from bivariate and multivariate analysis.

After adjustment of factors using multivariable logistic regression analysis, twelve factors were found to be significantly associated with the MDR-TB occurrence

Table 2 Clinical conditions of patients

Conditions	Number	Percentage	DS-TB($n=181$)		MDR-TB($n=181$)	
Clinical	***N***	**%**	***N***	**%**	***N***	**%**
Hospitalization history						
No	285	78.7	143	79.0	142	43.6
Yes	77	21.3	38	21.0	39	11.6
Tuberculosis history						
No	286	79.0	162	89.5	124	49.4
Yes	76	21.0	19	10.5	57	5.8
MDR-TB history						
No	335	92.5	181	100.0	154	55.2
Yes	27	7.5	0	0.0	27	0.0
Failure history						
No	323	89.2	163	90.1	160	49.8
Yes	39	10.8	18	9.9	21	5.5
After the first line TT						
No	332	91.7	181	100.0	151	55.2
Yes	30	8.3	0	0.0	30	0.0
After the second line TT						
No	359	99.2	181	100.0	178	55.2
Yes	3	0.8	0	0.0	3	0.0
Regularity TT						
No	320	88.4	163	90.1	157	49.8
Yes	42	11.6	18	9.9	24	5.5
PTB close contact						
No	287	79.3	162	89.5	125	49.4
Yes	75	20.7	19	10.5	56	5.8
MDR-TB Close contact						
No	306	84.5	176	97.2	130	53.7
Yes	56	15.5	5	2.8	51	1.5
Visits before TBDX						0
1	57	15.8	39	21.5	18	11.9
2	118	32.6	56	30.9	62	17.1
3	108	29.8	48	26.5	60	14.7
4	32	8.8	12	6.6	20	3.7
5	23	6.4	13	7.2	10	4.0
6	15	4.1	9	5.0	6	2.7
10	9	2.5	4	2.2	5	1.2
Clinical condition at T3 initiation						
Stable	201	55.5	108	59.7	93	33.0
Unstable	161	44.5	73	40.3	88	22.3
TB Type						
EPTB	30	8.3	15	8.3	15	4.6
PTB	332	91.7	166	91.7	166	50.7
Site of EPTB						
Abdominal	1	0.3	0	0.0	1	0.0
Lymph nodes	10	2.8	7	3.9	3	2.1
Pleural Effusion	19	5.3	8	4.4	11	2.4
Treatment supporter						
No	175	48.3	81	44.8	94	24.7
Yes	187	51.6	100	55.2	87	30.5

Table 2 (continued)

Conditions	Number	Percentage	DS-TB($n=181$)		MDR-TB($n=181$)	
Clinical	***N***	**%**	***N***	**%**	***N***	**%**
HIV status						
Negative	235	64.9	121	66.9	114	36.9
Positive	127	35.1	60	33.1	67	18.3
CPT intake						
Yes	127	100%	60	33.1	67	18.3
ART_intake				0.0		0.0
Yes	122	33.7	58	32.0	64	17.7
ART regimen						
ABC/3 TC/EFV	1	0.3	0	0.0	1	0.0
AZT/3 TC/ATV	1	0.3	1	0.6	0	0.3
AZT/3 TC/EFV	2	0.6	1	0.6	1	0.3
TDF/3 TC/ATV	4	1.1	2	1.1	2	0.6
TLD	89	24.6	40	22.1	49	12.2
TLE	28	7.7	16	8.8	12	4.9
Treatment outcome (death)				0.0		0.0
Yes	58	16.1	30	16.6	28	9.2
No	304	84.0	150	82.9	154	45.8
Time to death (in days)						
Early mortality [≤ 60 days]	43	70.1	21	48.8	22	51.2
Late mortality [> 60 days]	15	29.9	9	60.0	6	40.0

(Table 4).These factors were the COVID-19 period (aOR: 1.8, 95% CI: 1.02–3.3), low educational level (primary or less) (aOR: 3.9, 95% CI: 1.5–10.9), rural residence (aOR: 4.1, 95% CI: 1.9–9.0), unemployment (aOR: 4.5, 1.9–11.8), more than six household's members (5.8, 95% CI: 2.9,11.9), more than two member in the room, public transport (aOR: 2.219, 95% CI: 1.21–4.15), MDR-TB close contact (aOR: 31.54, 95% CI: 11.49–105.84), tobacco consumption (aOR: 10.22, 95% CI: 4.86–22.75), comorbidity with diabetes (aOR: 11.67, 95% CI: 2.67, 68.59) and late diagnostic (aOR: 2.262, 96% CI: 1.04, 5.14). The table below shows the final model resulting from a multivariate model selected using the Bayesian Information Criterion-based backward and parsimony principal methods. The table below shows the final.

Discussion

Globally, the TB mortality and the growing threat of MDR-TB constitute a major public health challenge. Given the unprecedented disruptions of COVID-19, we need to understand how the pandemic held back Burundi progress towards WHO's targets to End TB. This study sought to investigate TB related mortality and MDR risk in the context of COVID-19 pandemic in Burundi.

The TB-related mortality varied from DS-TB patients to MDR-TB patients, and from the pre-COVID-19 pandemic period to COVID-19 pandemic period. MDR-TB related mortality significantly increased during COVID-19 period. Factors such as low education level, high household size, high number of room members, public transport, rural residence, tobacco smoking, MDR-TB close contact, COVID-19 pandemic, occupation, delay in TB diagnostic, collective residence and diabetes underlying condition were found to be significantly associated with MDR-TB infection occurrence.

During COVID-19, the overall TB related mortality did not significantly increased [50]. These findings are consistent with recent study conducted in Indonesia, which similarly reported no significant rise in all-cause mortality compared to the pre-pandemic [51]. This could be due to the decrease in reported TB cases observed during COVID-19 [50, 52]. Indeed, the impact of COVID-19 was projected to cause 9-year setback in TB detection [53, 54].

Despite these variations, the COVID-19 pandemic adversely affected the national tuberculosis programs globally, including in Burundi [51, 55, 56]. In Burundi, MDR-TB -related mortality significantly increased during COVID-19 pandemic period. The risk of MDR-TB was also higher during COVID-19 pandemic than before. These findings are consistent with other studies reporting that COVID-19 significantly contributed to the increased TB morbidity and TB-related mortality [51, 57, 58]. A recent scoping review further highlighted

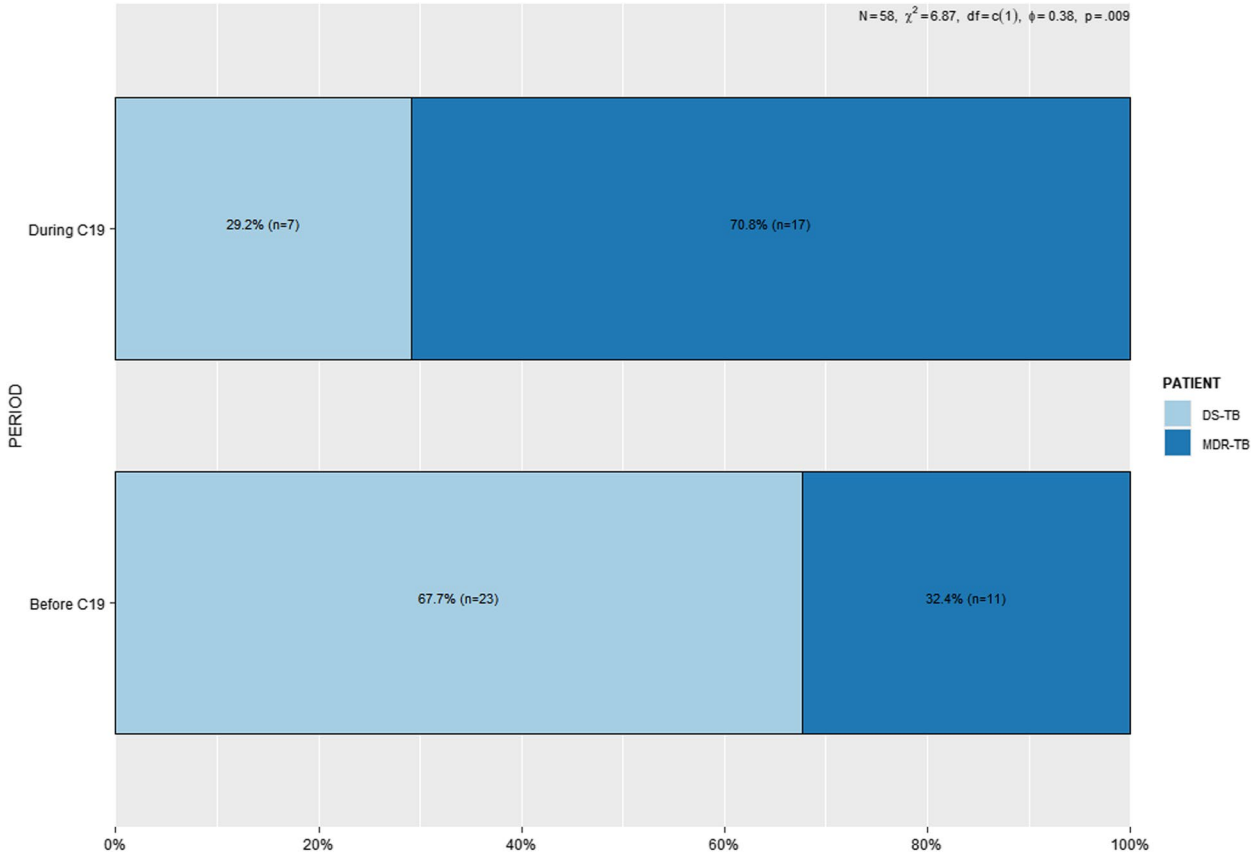

Fig. 2 TB related mortality between July 2018 and November 2022 in Burundi

that the COVID-19 pandemic has increased MDR-TB incidence in LMICs [59].

This could be due to the reduction of TB treatment coverage observed during COVID-19 in countries with low health-system capacity, such as Burundi [51]. Additionally, factors such as COVID-19 airborne transmission, absence of COVID-19 screening in MDR-TB patients before hospitalization, healthcare workers and families members, and absence of sufficient respiratory isolation rooms in low resources settings such as Burundi, with only 1 MDR-TB referral hospital for MDR-TB management, may increase the within hospital COVID-19 spread and MDR-TB patients vulnerability [60]. Although this study did not specifically focus on MDR-TB and COVID-19 coinfection, recent studies that COVID-19 symptoms, such as nausea and vomiting, may challenge MDR-TB treatment adherence [61, 62].

Patients with lower educational levels, living in rural areas, living in collective residences, being unemployed, living in high-sized households, high number of people (> 2) by room were more likely to have TB in general. They were more likely to develop MDR infections. All these factors are key indicators of low socio-economic status, which has consistently been associated with TB risk in priors studies [59, 63]. Another study conducted in Lesotho similarly showed that TB disproportionally affects people with low socioeconomic status [15]. Likewise, studies conducted East Shoa, Ethiopia highlighted the association between rural residency and increased MDR-TB risk [64]. The high proportion of rural residents, limited access to TB services, socioeconomic disparities and the low level of awareness regarding adherence to first-line TB treatment in rural communities may contribute to the burden of MDR-TB [64].

Unemployed individuals and low-income earners were reported to be more likely to develop MDR-TB than employed and high-income earners [65]. Previous studies conducted in the mining communities of Marerani in Tanzania [66], as well as a recent systematic review and meta-analysis conducted in LMICs identified a strong association between MDR-TB and low socio-economic status, particularly during COVID-19 pandemic [59].

Close contact with individuals diagnosed with MDR-TB was another important predictor of MDR-TB infection, a finding consistent with findings from recent studies in the Democratic Republic of Congo

Table 3 Bivariate and multivariable logistic regression analysis of patients with tuberculosis

Models		**Bivariate models**			**Multivariate Model**		
Conditions	***N***	**OR**	**95% CI**	***p***	**aOR**	**95% CI**	***p***
Socio-demographic							
Period							
Before C19	222	Ref			Ref		
During C19	140	1.67	[1.09, 2.57]	0.018	1.83	[1.01, 3.40]	0.051
Education level							
University	34	Ref			Ref		
Primary or less	219	2.06	[0.99, 4.50]	0.059	3.930	[1.38, 12.03]	0.013
Secondary	109	1.74	[0.79, 3.95]	0.176	2.457	[0.83, 07.72]	0.112
Residence							
Rural	93	Ref			Ref		
Urban	269	2.37	[1.46, 3.90]	< 0.001	4.13	[1.88,09.46]	0.001
Living conditions							
Prior incarceration							
No	343	Ref			Ref		
Yes	19	3.99	[1.42,14.24]	0.016	2.01	[0.38,13.47]	0.406
Collective residence							
No	325	Ref			Ref		
Yes	37	3.49	[1.66, 8.07]	0.002	2.33	[0.83, 6.89]	0.115
Occupation1							
Empoyed	53	Ref			Ref		
Unemployed	309	2.94	[1.58, 5.72]	< 0.001	4.31	[1.71,11.75]	0.003
Household size							
≤ 6	273	Ref			Ref		
> 6	89	3.94	[2.35, 6.83]	< 0.001	6.31	[3.13,13.32]	< 0.001
Persons by room							
1–2	194	Ref			Ref		
3 +	168	1.34	[0.88, 2.02]	0.171	1.86	[0.94, 3.77]	0.080
Public transport							
No	180	Ref			Ref		
Yes	182	1.70	[1.13, 2.59]	0.012	2.14	[1.12, 4.16]	0.023
Clinical conditions	N	OR	95% CI	p	aOR	95% CI	p
TB history							
No	286	Ref			Ref		
Yes	76	3.92	[2.25, 7.08]	< 0.001	2.19	[0.02, 264.9]	0.746
PTB close contact							
No	287	Ref			Ref		
Yes	75	3.72	[2.14, 6.73]	< 0.001	0.51	[0.01,34.44]	0.764
MDR-TB close contact							
No	306	Ref			Ref		
Yes	56	13.81	[5.88,40.55]	< 0.001	36.07	[12.58,1269]	< 0.001
Tobacco smoking							
No	282	Ref			Ref		
Yes	80	4.33	[2.51, 7.81]	< 0.001	3.88	[0.25,114.79]	0.356
Alcohol							
No	286	Ref			Ref		
Yes	76	3.92	[2.25, 7.08]	< 0.001	1.26	[0.12, 10.89]	0.835
Diabetes							
No	346	Ref			Ref		

Table 3 (continued)

Models		Bivariate models			Multivariate Model		
Conditions	***N***	**OR**	**95% CI**	***p***	**aOR**	**95% CI**	***p***
Yes	16	4.59	[1.45,20.28]	0.019	12.97	[2.64, 84.15]	0.003
Nutritional status							
Normal	144	Ref			Ref		
M.malnutrition	129	0.74	[0.21, 2.42]	0.616	1.36	[0.26, 6.66]	0.706
S.malnutrition	89	1.07	[0.69, 1.65]	0.761	0.68	[0.35, 1.32]	0.256
Irregularity to T3							
No	297	Ref			Ref		
Yes	65	3.82	[2.19, 6.90]	< 0.001	2.21	[0.61, 8.26]	0.229
Visits before TB Dx							
1	57	Ref			Ref		
2 +	315	2.49	[1.39, 4.63]	< 0.001	1.33	[0.73, 2.44]	0.355
Clinical condition at treatment start							
Stable	201	Ref			Ref		
Unstable	161	1.40	[0.92, 2.13]	0.113	1.41	[0.75, 2.67]	0.049
Treatment/supporter							
Yes	187	Ref			Ref		
No	175	1.34	[0.88, 2.02]	0.172	2.28	[1. 02, 5.28]	< 0.001
HIV Status							
Negative	235	Ref			Ref		
Positive	127	3.92	[2.25, 7.08]	< 0.001	-	-	-

(DRC) and India [67, 68]. Household transmission of drug-resistant TB was found to have increased during the pandemic in LMICs, potentially due to prolonged household exposure during lockdowns and limited access to TB services [59].

Tobacco smoking was also found to be significantly associated with MDR-TB infection. This finding is consistent with previous studies conducted in China, India, and Southern Ethiopia which highlighted a significant association between tobacco smoking and MDR-TB [69–71]. The association between tobacco smoking and MDR-TB in the context of COVID-19 pandemic has been well documented,particularly in low-income countries [72, 73, 59], and smoking has been shown to impair host immunity, thereby increasing susceptibility to infection and disease progression [74, 75].

Diabetes emerged as another important risk factor for MDR-TB.Patients with diabetes were more likely to develop MDR-TB infection than patients without diabetes, a trend also reported in recent studies conducted in Pakistan, China, and other LMICs [59, 76, 77]. Diabetes has been associated with increased TB severity, relapse rates, and drug resistance [78, 79]. The exacerbated chemo resistance due immune response and clinical deterioration among diabetic TB patients may explain the increased risk [79]. Another reason should be the polymorphism variation of glutathione-S-transferase genes among patients. Deletions or variations in these genes have been linked to impaired response to anti-TB therapy and reduced treatment efficacy [80].

Furthermore, patients with more than one healthcare visit before receiving a TB diagnosis were more likely to develop MDR-TB infection than those diagnosed during their first consultation. This indirectly suggests a potential delay in TB diagnosis, a known risk factor to drug resistance. Similar findings from two studies conducted in India showed that the delay in referral for the diagnosis as well as in the initiation of anti-TB treatment were significantly associated with TB drug resistance [75, 81].

The current study successfully achieved its primary objective of assessing TB-related mortality and MDR-TB risks in the context of the COVID-19 pandemic in Burundi. Findings contribute to the evolving understanding of the indirect effects of COVID-19 pandemic on TB and MDR-TB control and highlight critical socioeconomic and health system challenges. They also provide important recommendations to the stakeholders as well as the Burundian government to strengthen TB program and pandemic preparedness, supporting the broader Global efforts to End TB by 2035.

This study has some restrictions on TB/MDR-TB and COVID-19 co-infection data availability. It excludes patients who did not seek treatment or were unable to access healthcare services during the pandemic. It

Table 4 Final model

Factors	*N* = 362	aOR	95% CI	*p*
Period				
Before COVID-19	222	Ref [aOR = 1]		
During COVID-19	140	1.82	[1.02, 3.28]	0.044
Education level				
University	34	Ref [aOR = 1]		
Primary or less	219	3.86	[1.45, 10.97]	0.009
Secondary	109	2.39	[0.85, 7.11]	0.106
Residence				
Rural	93	Ref [aOR = 1]	Ref	
Urban	269	4.11	[1.94, 9.02]	< 0.001
Collective residence				
No	325	Ref [aOR = 1]	Ref	
Yes	37	2.17	[0.81, 6.09]	0.129
Occupation				
Employed	53	Ref [aOR = 1]		
Unemployed	309	4.54	[1.89, 11.85]	0.001
Household size				
≤ 6	273	Ref [aOR = 1]		
> 6	89	5.76	[2.92, 11.88]	< 0.001
Persons by room				
1–2	25	Ref [aOR = 1]		
3 +	168	1.869	[0.97, 3.66]	0.063
Public transport				
No	180	Ref [aOR = 1]		
Yes	182	2.22	[1.21, 4.15]	0.011
MDR-TB close contact				
No	306	Ref [aOR = 1]		
Yes	56	31.54	[11.49, 105.84]	< 0.001
Tobacco smoking				
No	282	Ref [aOR = 1]		
Yes	80	10.22	[4.86, 22.75]	< 0.001
Diabetes				
No	346	Ref [aOR = 1]		
Yes	16	11.67	[2.67, 68.59]	0.002
Visits before TB Dx				
1	57	Ref [aOR = 1]		
2 +	315	2.26	[1.04, 5.14]	0.045

doesn't include TB patients in others health facility across the country. While the study identifies several factors associated with MDR-TB risk, there may be additional confounding variables that were not considered or controlled for in the analysis such as access to healthcare and healthcare infrastructure. Wealth index, which could impact the outcomes, and opinions of patients and staff were not explicitly addressed in the Study.

A mixed methods study involving a small sample of TB clinic staff and/or patients could provide valuable insights into the challenges faced in accessing healthcare services during the pandemic. This supplementary qualitative data could help clarify potential reasons behind increased mortality, case numbers, and MDR-TB incidences. Given the similarity in the demographic profiles of patients before and during the pandemic, the qualitative data could tease out differences that were not apparent in the quantitative analysis. In addition, support network at household and community levels as well as health literacy should be considered.

Future research should also investigate early TB-related mortality during the intensive phase of treatment, as well as use of new technologies for MDR-TB risk prediction during routine follow-up [82].

Policy implication

Findings from this study feed into Burundian context findings and can inform public health policies and interventions for pandemic preparedness. Understanding how the pandemic affected TB control efforts can help in development of strategies to mitigate the impact of future health crises on existing TB program. Public health intervention should focus on intensive phase of treatment and identified risk factors, particularly socioeconomic determinants, as well as on practical recommendations by teaching household members about the prevention of two infectious diseases. Priority of TB prevention should focus on development of new TB vaccines as recommended by all governments at the United Nations General assembly High Level meeting in New York in September 2023 [83]. Focus should also be on support network, health literacy, as well as person-centered, equity-oriented approach to ending tuberculosis in a post-COVID-19 world [56]. Continued support for TB program should be essential to sustain progress, prevent further setbacks, and protect the most vulnerable populations.

Conclusion

TB-related mortality as well as MDR-TB infection risk increased during COVID-19. They were observed particularly among patients with a low socio-economic status. Indeed, MDR-TB risk factors include socio-demographics, living, clinical, and therapeutic conditions.

This situation raises a cause for concern, especially in this context where there exists an equally high burden of communicable and no communicable diseases including malnutrition in Burundi. A holistic approach focused on these identified factors could go a long way in a TB-free environment in the understudied areas in Burundi.

Abbreviations

COVID-19	Coronas Virus Disease 19
TB	Tuberculosis
MDR-TB	Multidrug-Resistance Tuberculosis
LICs	Low-Income Countries
LMICs	Low and Middle-Income Countries
WHO	World Health Organization
DS-TB	Drug Susceptible Tuberculosis
CATB	Centre anti tuberculeux de Bujumbura
DRC	Democratic Republic of Congo
MTB	Mycobacterium tuberculosis
RIF	Rifampicin
VIF	Variance Inflation Factors
BIC	Bayesian Information Criterion
Before C19	Before COVID-19
CI	Confidence Interval
GVIF	Generalized Variance Information Factor
ROC	Receiving Operating Characteristics
AUC	Area Under curve
DRC	Democratic Republic of Congo
CPT	Chemoprophylaxis treatment
PTB	Pulmonary Tuberculosis
HIV	Human Immunodeficiency Virus
ART	Anti-Retroviral Treatment
TLD	Tenofovir-Lamivudine -Dolutegravir
aOR	Adjusted Odds Ratio
OR	Odds Ratio
Ref	Reference
IRB	Institutional Review Board
TT	Treatment

Acknowledgements
The authors do acknowledge all the support rendered by Burundian Health facilities and Harvard University. This project was conducted with the support of the Takemi Program in International Health at the Harvard T.H. Chan School of Public Health. Authors do also acknowledge the contributions of Professor Stephane Verguet, Professor Goto Aya,Jesse Bump and Professor Michael Reich.

Clinical trial number
Not applicable.

Authors' contributions
AI conceptualized the study, designed the methodology, and did preliminary analysis. FG and ENO supervised the work. ENO and AI curated the analysis and design for all intellectual content and approved the final version for publication. AI agreed to be pivotal in any correspondence to do with any intellectual content of the study. He is the corresponding author, for this matter.

Funding
No external funding was available for this study.

Data availability
The dataset related to this study is available with the corresponding author and can be available on reasonable request.

Declarations

Ethics approval and consent to participate
The study was approved by an institutional ethics committee of Kamenge Teaching Hospital (N/Ref.2022/DGCHUK836/11.5). The study met the criteria for exemption from the regulations found at 45 CFR46.104(d) (4). No informed consent was needed. The Harvard T.H. Chan School of Public Health IRB office (RB23-1209) has, additionally, waived the requirement for informed consent. All data were fully anonymized before we accessed them. The study was conducted by the guidelines of the Declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Global Health and Population, Takemi Program in International Health, Harvard T.H. Chan School of Public Health, P.O. Box 02144, Boston, MA, USA. [2]Department of Medicine, Kamenge Teaching Hospital, University of Burundi, P.0.Box 1020, Bujumbura, Burundi. [3]National Data Management Center for Health, Ethiopian Public Health Institute, P.O. Box 5645, Addis Ababa, Ethiopia. [4]Department of Medicine, School of Clinical Sciences, Monash University, Wellington Rd, P.O. Box 3168, Clayton, VIC, Australia.

Received: 8 January 2025 Accepted: 7 May 2025
Published online: 17 May 2025

References

1. World Health Organization. Global tuberculosis report 2024. Geneva: WHO; 2024. Available from: https://www.who.int/teams/global-programme-on-tuberculosis-and-lung-health/tb-reports/global-tuberculosis-report-2024.
2. World Health Organization. WHO global lists of high burden countries for tuberculosis (TB), TB/HIV and multidrug/ rifampicin-resistant TB (MDR/RR-TB), 2021–2025: background document. Geneva. World Health Organization (https://apps.who.int/iris/handle/10665/341980).
3. Thornton J. Don't forget chronic lung and immune conditions during covid-19, says WHO. In.: British Medical Journal Publishing Group; 2020.
4. Chakaya J, Khan M, Ntoumi F, Aklillu E, Fatima R, Mwaba P, Kapata N, Mfinanga S, Hasnain SE, Katoto PD: Global Tuberculosis Report 2020–Reflections on the Global TB burden, treatment and prevention efforts. Int J Infect Dis. 2021.
5. Bagcchi S. WHO's global tuberculosis report 2022. Lancet Microbe. 2023;4(1):e20.
6. Faisal S. Global Tuberculosis Epidemiology. In: Cardona P-J, Gagneux S, éditeurs. Tuberculosis: Integrated Studies for a Complex Disease. Cham: Springer; 2023. p. 17–31. https://doi.org/10.1007/978-3-031-15955-8_2.
7. McQuaid CF, Vassall A, Cohen T, Fiekert K, White RG. The impact of COVID-19 on TB: a review of the data. Int J Tuberc Lung Dis. 2021;25(6):436–46.
8. Visca D, Ong C, Tiberi S, Centis R, D'ambrosio L, Chen B, Mueller J, Mueller P, Duarte R, Dalcolmo M. Tuberculosis and COVID-19 interaction: a review of biological, clinical and public health effects. Pulmonology. 2021;27(2):151–65.
9. Mousquer GT, Peres A, Fiegenbaum M. Pathology of TB/COVID-19 co-infection: the phantom menace. Tuberculosis. 2021;126:102020.
10. Migliori GB, Nardell E, Yedilbayev A, D'Ambrosio L, Centis R, Tadolini M, Van Den Boom M, Ehsani S, Sotgiu G, Dara M. Reducing tuberculosis transmission: A consensus document from the World Health Organization Regional Office for Europe. Eur Respir J. 2019;53(6):1900391. https://doi.org/10.1183/13993003.00391-2019.
11. Shariq M, Sheikh JA, Quadir N, Sharma N, Hasnain SE, Ehtesham NZ. COVID-19 andtuberculosis: The double whammy of respiratory pathogens. Eur Respir Rev. 2022;31(164):210264. https://doi.org/10.1183/16000617.0264-2021.
12. Haacker M. Contributions of declining mortality, overall and from HIV, TB and malaria, to reduced health inequality and inequity across countries. Health Policy Plan. 2023;38(8):939–48.
13. Horton R. Offline: COVID-19 and the convergence of nations. The Lancet. 2021;397(10273):458.
14. Dara M, Sotgiu G, Reichler M, Chiang C, Chee C, Migliori G. New diseases and old threats: lessons from tuberculosis for the COVID-19 response. Int J Tuberc Lung Dis. 2020;24(5):544–5.
15. Andom AT, Fejfar D, Yuen CM, Ndayizigiye M, Mugunga JC, Mukherjee JS. The Impact of COVID-19 on Tuberculosis Program Performance in the Kingdom of Lesotho. Tropical Med Infect Dis. 2023;8(3):165.
16. Alene KA, Wangdi K, Clements AC. Impact of the COVID-19 pandemic on tuberculosis control: an overview. Tropical Med Infect Dis. 2020;5(3):123.
17. Lancet T. Tackling poverty in tuberculosis control. Lancet. 2005;366(9496):2063.

18. World Health Organization. WHO consolidated guidelines on tuberculosis. Module 2: screening-systematic screening for tuberculosis disease. Geneva: World Health Organization; 2021.
19. World Health Organization. (2023). Global Tuberculosis Report 2023. Geneva: WHO.https://www.who.int/publications/i/item/9789240083851.
20. Shibabaw A, Gelaw B, Gebreyes W, Robinson R, Wang SH, Tessema B. The burden of pre-extensively and extensively drug-resistant tuberculosis among MDR-TB patients in the Amhara region, Ethiopia. PLoS ONE. 2020;15(2):e0229040.
21. Lessem E. Tuberculosis drug development hobbles forward. HIV• HCV• TB. 2014;197.
22. Stop TB Partnership. HIV and Tuberculosis: Factsheet. Geneva: Stop TB Partnership; 2015.
23. Kizito E, Musaazi J, Mutesasira K, Twinomugisha F, Namwanje H, Kiyemba T, Lopez DBF, Nicholas NS, Nkolo A, Birabwa E. Risk factors for mortality among patients diagnosed with multi-drug resistant tuberculosis in Uganda-a case-control study. BMC Infect Dis. 2021;21(1):1–7.
24. Fukunaga R, Glaziou P, Harris JB, Date A, Floyd K, Kasaeva T. Epidemiology of Tuberculosis and Progress Toward Meeting Global Targets—Worldwide, 2019. Morb Mortal Wkly Rep. 2021;70(12):427.
25. World Bank. Learning from Burundi's Political Pivot on COVID-19 Vaccines. Available online: https://blogs.worldbank.org/nasikiliza/learning-burundis-political-pivot-covid-19-vaccines
26. Xinhua. Burundi extends quarantine to travelers from U.S., Britain, Australia and China. 2020. Available from:http://www.china.org.cn/world/Off_the_Wire/2020-03/17/content_75824457.htm.
27. Tasamba J. Travelers to Burundi to be quarantined for coronavirus . Anadolu Agency; 2020. Available from: https://www.aa.com.tr/en/africa/travelers-to-burundi-to-be-quarantined-for-coronavirus/1764008. Cited 2025 Apr 14.
28. Reuters. Burundi launches COVID-19 vaccination drive . Reuters; 2021. Available from: https://www.reuters.com/world/africa/burundi-launches-covid-19-vaccination-drive-2021-10-18/. Cited 2025 Apr 14.
29. Nalunjogi J, Mucching-Toscano S, Sibomana JP, Centis R, D'Ambrosio L, Alffenaar J-W, Denholm J, Blanc F-X, Borisov S, Danila E: Impact of COVID-19 on diagnosis of tuberculosis, multidrug-resistant tuberculosis, and on mortality in 11 countries in Europe, Northern America, and Australia. A Global Tuberculosis Network study. Int J Infect Dis. 2023;130:S25-S29.
30. Wekunda PW, Kosgei RJ, Gathara D, Maore N, Masini E, Omesa EN, Kimenye K. Evaluation of treatment outcomes and associated factors among patients managed for tuberculosis in Vihiga County, 2012–2015. East Afr Med J. 2017;94(10):S18–27.
31. Abdullahi OA, Ngari MM, Sanga D, Katana G, Willetts A. Mortality during treatment for tuberculosis; a review of surveillance data in a rural county in Kenya. PLoS ONE. 2019;14(7):e0219191.
32. Kosgei RJ, Callens S, Gichangi P, Temmerman M, Kihara A-B, David G, Omesa EN, Masini E, Carter EJ. Gender difference in mortality among pulmonary tuberculosis HIV co-infected adults aged 15–49 years in Kenya. PLoS ONE. 2020;15(12):e0243977.
33. Akhtar AM, Kanwal S, Majeed S, Majeed W. Weight variation increases the risk of death during the intensive phase of treatment among MDR-TB patients: A retrospective study. Pakistan J Med Sci. 2023;39(4):1080.
34. Musaazi J, Sekaggya-Wiltshire C, Kiragga A, Kalule I, Reynolds S, Manabe Y, Castelnuovo B. Sustained positive impact on tuberculosis treatment outcomes of TB-HIV integrated care in Uganda. Int J Tuberc Lung Dis. 2019;23(4):514–21.
35. Chakaya J, Khan M, Ntoumi F, Aklillu E, Fatima R, Mwaba P, Kapata N, Mfinanga S, Hasnain SE, Katoto PD. Global Tuberculosis Report 2020–Reflections on the Global TB burden, treatment and prevention efforts. Int J Infect Dis. 2021;113:S7–12.
36. Ciza F, Gils T, Sawadogo M, Decroo T, Roggi A, Piubello A, Ortuño-Gutiérrez N. Course of adverse events during short treatment regimen in patients with rifampicin-resistant tuberculosis in Burundi. J Clin Med. 2020;9(6):1873.
37. Jee Y. WHO International Health Regulations Emergency Committee for the COVID-19 outbreak. Epidemiol Health. 2020;42:e2020013. https://doi.org/10.4178/epih.e2020013.
38. Fahim NK, Negida A, Fahim AK. Sample Size Calculation Guide - Part 3: How to Calculate the Sample Size for an Independent Case-control Study. Adv J Emerg Med. 2019;3(2):e20.
39. Nicholson TJ, Hoddinott G, Seddon JA, Claassens MM, van der Zalm MM, Lopez E, Bock P, Caldwell J, Da Costa D, de Vaal C. A systematic review of risk factors for mortality among tuberculosis patients in South Africa. Syst Rev. 2023;12(1):23.
40. Zanke AA, Thenge RR, Adhao VS. COVID-19: A pandemic declare by world health organization. IP Int J Compr and Adv Pharmacol. 2020;5(2):49–57.
41. Kamble T, Kashid D, Sakate D. Consistent and robust variable selection in regression based on Wald test. Commun Stat Theory Methods. 2019;48(8):1981–2000.
42. Bursac Z, Gauss CH, Williams DK, Hosmer DW. Purposeful selection of variables in logistic regression. Source Code Biol Med. 2008;3:17.
43. Mohammad Ziaul Islam C, Tanvir CT. Variable selection strategies and its importance in clinical prediction modelling. Family Med Commun Health. 2020;8(1):e000262.
44. Hosmer DW Jr, Lemeshow S, Sturdivant RX. Applied Logistic Regression. 3rd ed. Hoboken, NJ: John Wiley & Sons; 2013.
45. Kyriazos T, Poga M. Dealing with Multicollinearity in Factor Analysis: The Problem, Detections, and Solutions. Open J Stat. 2023;13(3):404–24.
46. Chicco D, Jurman G. The Matthews correlation coefficient (MCC) should replace the ROC AUC as the standard metric for assessing binary classification. BioData Mining. 2023;16(1):1–23.
47. de Hond AA, Steyerberg EW, van Calster B. Interpreting area under the receiver operating characteristic curve. Lancet Digital Health. 2022;4(12):e853–5.
48. Zhang X, Liu C-A. Model averaging prediction by K-fold cross-validation. J Econom. 2023;235(1):280–301.
49. He Q, Zhang M, Zhang J, Yang S, Wang C: K-Fold Cross-Valuation for Machine Learning Using Shapley Value. In: *International Conference on Artificial Neural Networks: 2023*: Springer; 2023: 50–61.
50. Kyu HH, Ledesma JR. What is the impact of the COVID-19 pandemic on tuberculosis? Lancet Glob Health. 2023;11(9):e1323–4.
51. Surendra H, Elyazar IR, Puspaningrum E, Darmawan D, Pakasi TT, Lukitosari E, Sulistyo S, Deviernur SM, Fuady A, Thwaites G. Impact of the COVID-19 pandemic on tuberculosis control in Indonesia: a nationwide longitudinal analysis of programme data. Lancet Glob Health. 2023;11(9):e1412–21.
52. Arentz M, Ma J, Zheng P, Vos T, Murray CJ, Kyu HH. The impact of the COVID-19 pandemic and associated suppression measures on the burden of tuberculosis in India. BMC Infect Dis. 2022;22(1):92.
53. Trajman A, Felker I, Alves LC, Coutinho I, Osman M, Meehan S, Singh U, Schwartz Y. The COVID-19 and TB syndemic: The way forward. Int J Tuberc Lung Dis. 2022;26(8):710–9.
54. Abdullah MU, Imran A, Saulat A, Asmat F, Nadeem S, Ramzan M, Rafique MH, Rafique R. Socioeconomic Determinants of Pulmonary Tuberculosis during Covid-19 Pandemic: Case Control Study. Pakistan J MedHealth Sci. 2023;17(06):121–121.
55. Nalunjogi J, Mucching-Toscano S, Sibomana JP, Centis R, D'Ambrosio L, Alffenaar J-W, Denholm J, Blanc F-X, Borisov S, Danila E. Impact of COVID-19 on diagnosis of TB, MDR-TB and on mortality in 11 countries in Europe, northern America and Australia: a Global Tuberculosis Network study. Int J Infect Dis. 2023;1:S25-S29. https://doi.org/10.1016/j.ijid.2023.02.025.
56. Ryckman T, Robsky K, Cilloni L, Zawedde-Muyanja S, Ananthakrishnan R, Kendall EA, Shrestha S, Turyahabwe S, Katamba A, Dowdy DW. Ending tuberculosis in a post-COVID-19 world: a person-centred, equity-oriented approach. Lancet Infect Dis. 2023;23(2):e59–66.
57. Koupaei M, Naimi A, Moafi N, Mohammadi P, Tabatabaei FS, Ghazizadeh S, Heidary M, Khoshnood S. Clinical characteristics, diagnosis, treatment, and mortality rate of TB/COVID-19 coinfectetd patients: a systematic review. Front Med. 2021;8:2188.
58. Easton AV, Salerno MM, Trieu L, Humphrey E, Kaba F, Macaraig M, Dworkin F, Nilsen DM, Burzynski J. Cohort study of the mortality among patients in New York City with tuberculosis and COVID-19, March 2020 to June 2022. PLOS Global Public Health. 2023;3(4):e0001758.
59. Ichsan I, Redwood-Campbell L, Mahmud NN, Dimiati H, Yani M, Mudatsir M, Syukri M. Risk factors of MDR-TB and impacts of COVID-19 pandemic on escalating of MDR-TB incidence in lower-middle-income countries: A scoping review. Narra J. 2023;3(2):e220–e220.
60. Motta I, Centis R, D'Ambrosio L, García-García J-M, Goletti D, Gualano G, Lipani F, Palmieri F, Sánchez-Montalvá A, Pontali E. Tuberculosis, COVID-19 and migrants: preliminary analysis of deaths occurring in 69 patients from two cohorts. Pulmonology. 2020;26(4):233–40.

61. Goyal P, Choi JJ, Pinheiro LC, Schenck EJ, Chen R, Jabri A, Satlin MJ, Campion TR Jr, Nahid M, Ringel JB. Clinical characteristics of Covid-19 in New York city. N Engl J Med. 2020;382(24):2372–4.
62. Vilbrun SC, Mathurin L, Pape JW, Fitzgerald D, Walsh KF. Case Report: Multidrug-Resistant Tuberculosis and COVID-19 Coinfection in Port-au-Prince. Haiti Am J Trop Med Hyg. 2020;103(5):1986–8.
63. Liu Y, Cao D, Cao X, Jain V, Chawla C, Shabbir MS, Ramos-Meza CS. The effects of MDR-TB treatment regimens through socioeconomic and spatial characteristics on environmental-health outcomes: evidence from Chinese hospitals. Energy Environ. 2023;34(4):1081–93.
64. Zereabruk K, Kahsay T, Teklemichael H, Aberhe W, Hailay A, Mebrahtom G, Bezabh G. Determinants of multidrug-resistant tuberculosis among adults undergoing treatment for tuberculosis in Tigray Region, Ethiopia: a case–control study. BMJ Open Respir Res. 2024;11(1):e001999.
65. Olabiyi OE, Okiki PA, Adarabioyo MI, Adebiyi OE, Adegoke OE, Esan OE, Idris OO, Agunbiade TB. Distribution of multi-drug resistant tuberculosis in Ekiti and Ondo states, Nigeria. New Microbes New Infect. 2023;53:101–92. https://doi.org/10.1016/j.nmni.2023.101192.
66. Mbuya AW, Mboya IB, Semvua HH, Mamuya SH, Msuya SE. Prevalence and factors associated with tuberculosis among the mining communities in Mererani, Tanzania. PLoS ONE. 2023;18(3):e0280396.
67. de Dieu Longo J, Woromogo SH, Tekpa G, Diemer HS-C, Gando H, Djidere FA, Grésenguet G. Risk factors for multidrug-resistant tuberculosis in the Central African Republic: a case control study. J Infect Public Health. 2023;9:1341–5. https://doi.org/10.1016/j.jiph.2023.06.007.
68. Vyawahare C, Mukhida S, Khan S, Gandham NR, Kannuri S, Bhaumik S. Assessment of risk factors associated with drug-resistant tuberculosis in pulmonary tuberculosis patients. Indian J Tuberc. 2023;71:S44–S51. https://doi.org/10.1016/j.ijtb.2023.07.007.
69. Tao N-n, Li Y-f, Song W-m, Liu J-y, Zhang Q-y, Xu T-t, Li S-j, An Q-q, Liu S-q, Li H-c. Risk factors for drug-resistant tuberculosis, the association between comorbidity status and drug-resistant patterns: A retrospective study of previously treated pulmonary tuberculosis in Shandong, China, during 2004–2019. BMJ Open. 2021;11(6):e044349.
70. Admassu F, Abera E, Gizachew A, Sedoro T, Gari T. Risk factors of multidrug resistant tuberculosis among patients with tuberculosis at selected multidrug resistance treatment initiative centres in southern Ethiopia: a case-control study. BMJ Open. 2023;13(1):e061836.
71. Mohite RV. Knowledge on the risk factors of drug-resistant tuberculosis among newly diagnosed patients of tuberculosis with first-line antitubercular treatment regimen. BLDE Univ J Health Sci. 2023;8:238–43. https://doi.org/10.4103/bjhs.bjhs_217_22.
72. World Health Organization. Global tuberculosis report 2013. Geneva: World Health Organization; 2013.
73. Muttamba W, Kirenga B, Ssengooba W, Sekibira R, Katamba A, Joloba ML. Prevalence of tuberculosis risk factors among bacteriologically negative and bacteriologically confirmed tuberculosis patients from five regional referral hospitals in Uganda. Am J Trop Med Hyg. 2019;100(2):386.
74. Irawan B, Sumardiyono S, Murti B. Meta-Analysis: Smoking and Proverty as Risk Factors of Tuberculosis Multidrug Resistance. J Health Promotion Behav. 2022;7(4):284–98.
75. Goel S, Bhatt G. The unequivocal relationship between tuberculosis and tobacco: integration of two maladies. In: Tuberculosis: Integrated Studies for a Complex Disease. Springer; 2023. p. 59–78. https://doi.org/10.1007/978-3-031-15955-8.
76. Khattak M, Mushtaq U, Latif M, Ahmad I, Rasool MF, Shakeel S, Hayat K, Hussain R, Alhazmi GA, Alshomrani AO. The impact of diabetes mellitus on the emergence of multi-drug resistant tuberculosis and treatment failure in TBdiabetes comorbid patients: a systematic review and meta-analysis. Front Public Health. 2023;11:1244450. https://doi.org/10.3389/fpubh.2023.1244450.
77. Chen Y, Liu J, Zhang Q, Chen H, Chai L, Wang Y, Zhang J, Qiu Y, Shen N, Shi X. Global burden of MDR-TB and XDRTB attributable to high fasting plasma glucose from 1990 to 2019: a retrospective analysis based on the global burden of disease study 2019. Eur J Clin Microbiol Infect Dis. 2024;43(4):747–65. https://doi.org/10.1007/s10096-024-04779-x.
78. Liberty P, Liberty M. Type 2 diabetes mellitus and pulmonary tuberculosis: literature review of a bidirectional relationship. Scripta Score Sci Med J. 2023;5(1). https://doi.org/10.32734/scripta.v5i1.11517.
79. Goletti D, Pisapia R, Fusco F, Aiello A, Van Crevel R. Epidemiology, pathogenesis, clinical presentation and management of TB in patients with HIV and diabetes. Int J Tuberc Lung Dis. 2023;27(4):284–90.
80. Semianiv I, Todoriko L, Semianiv M, Garas M, Todoriko L. Predicting the efficiency of the treatment of comorbidity diabetes mellitus and multidrug-resistant tuberculosis depending on the polymorphism variation of glutathione-S-transferase genes. Eur Respir J. 2023;62(suppl 67):PA2958. https://doi.org/10.1183/13993003.congress-2023.PA2958.
81. Jagtap J, Atre S, Dumbare Y, Faqih M, Sawant T, Ambike S, Bhawalkar J, Farhat M. Health system related barriers to multidrug-resistant tuberculosis (MDR-TB) care in an indian setting: from patients'perspective. Int J Infect Dis. 2023;130:S8.
82. World Health Organization (WHO). (2025, April 16). WHO consolidated guidelines on tuberculosis: Module 3: Diagnosis. WHO.https://www.who.int/publications/i/item/9789240107984.
83. da Costa C, Benn CS, Nyirenda T, Mpabalwani E, Grewal HM, Ahmed R, Kapata N, Nyasulu PS, Maeurer M, Hui DS: Perspectives on Development and Advancement of New Tuberculosis Vaccines. Int J Infect Dis. 2024:106987.

Publisher's Note