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Original article

High treatment success among individuals with rifampicin-resistant tuberculosis in Botswana: A retrospective cohort study

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ABSTRACT

Background: Rifampicin-resistant tuberculosis (RR-TB) remains a global health challenge, which is often characterized by limited treatment options and increased morbidity and mortality. Despite advances in diagnostics and the introduction of new drug regimens, treatment success for drug-resistant TB remains low. There is limited data on clinical, sociodemographic, and microbiological factors that influence patient outcomes. The aim of the study is to evaluate TB treatment outcomes among individuals diagnosed with RR-TB and to identify predictors of favourable and unfavourable treatment outcomes.

Methods: We conducted a retrospective study to analyse treatment outcomes of 162 individuals diagnosed with RR-TB using GeneXpert MTB/RIF and phenotypic drug susceptibility testing (pDST) from 2016 to 2023. Treatment outcome proportions were estimated using the binomial exact method with 95 % confidence intervals (CI). Predictors associated with unfavourable treatment outcomes were assessed using logistic regression models.

Results: Of the 162 individuals, 102(62.7 %) were male with a median age of 39 (interquartile range (IQR): 29–50). Most individuals, 78(48.1 %), were from the Greater Gaborone health district, and 88(54.3 %) were people living with HIV (PLWH). Among included individuals, 137(84.6 %, 95 % CI: 78.2–89.7) were successfully treated. Males had higher odds of unfavourable treatment outcomes compared to females (OR = 1.70; 95 % CI: 0.73–3.98). Among those cured, a slightly higher proportion was observed among PLWH (71.8 %, 95 % CI: 62.1–80.3) compared to people not living with HIV (PNLWH) (69.2 %, 95 % CI: 58.7–78.5). However, the mortality rate was higher among PLWH (10.7 %; 95 % CI: 5.5–18.3) than among PNLWH (6.6 %;

Abbreviations: ART, Antiretroviral therapy; BMI, Body mass index; CI, Confidence interval; CPT, Cotrimoxazole Preventive Therapy; DOTS, Direct Observed Therapy; DST, Drug susceptibility testing; ENA, European Nucleotide Archive; IQR, Interquartile range; LFU, Loss to follow-up; MDR-TB, Multi-drug-resistant tuberculosis; *Mtb*, *Mycobacterium tuberculosis*; PDST, phenotypic Drug Susceptibility Testing; PLWH, people living with HIV; PNLWH, people not living with HIV; Pre-XDR-TB, Pre-extensively drug-resistant tuberculosis; RR-TB, Rifampicin-Resistant Tuberculosis; TB, Tuberculosis; WHO, World Health Organisation

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95 % CI: 2.5–13.8). Those with a history of TB treatment had 1.03 odds of unfavourable treatment outcomes (95 % CI: 0.40–2.73); however, this association was not statistically significant.
Conclusion: Our study shows a high rate of successful treatment outcomes among individuals with RR-TB, with no significant difference based on sex, TB treatment history, or HIV status. Higher mortality among PLWH highlights the need for targeted interventions among high-risk groups.

Introduction

Tuberculosis (TB) remains one of the leading causes of death worldwide, despite being curable. The emergence and spread of Drug-resistant TB (DR-TB), particularly multidrug-resistant (MDR) or rifampicin-resistant (RR)-TB, has made TB prevention and treatment more complicated and challenging, posing a significant public health threat. In 2023, the World Health Organisation (WHO) reported an estimated 180,000 laboratory-confirmed MDR/RR-TB cases, with a global treatment success rate of 68 % [1], indicating persistent challenges in achieving optimal treatment outcomes. In the WHO African region, approximately 22,500 laboratory-confirmed RR/MDR-TB cases were reported in 2023, with a regional treatment success rate of 73 %, exceeding the WHO target [1, 2]. Botswana is amongst the top 30 high-TB/HIV burden countries and reports an estimated MDR/RR-TB incidence of 10 per 100,000 [1]. However, data on treatment outcomes among people with RR-TB remain limited. Treatment outcomes serve as critical indicators for assessing the effectiveness of TB prevention and care programs [3].

In Botswana, individuals diagnosed with RR-TB are treated using a standardised treatment regimen following the WHO and national treatment guidelines. In the standard treatment, a 9-month all-oral regimen, individuals receive bedaquiline, levofloxacin, linezolid, clofazimine, and cycloserine during the intensive phase, followed by levofloxacin, linezolid, clofazimine, and cycloserine for an additional 3–6 months during the continuation phase [4]. Botswana national DR-TB treatment guidelines adopted the WHO recommendations for all oral regimens [5]. However, some people may receive individualised treatment based on their previous TB history, adverse drug reactions, and drug susceptibility testing (DST) results [6]. Several clinical, demographic, and socio-economic factors influence treatment outcomes, including HIV infection, malnutrition, smoking, previous TB treatment, and diabetes [7–9]. Previous studies have highlighted age, sex, comorbidities, and body mass index (BMI) as key determinants of treatment success [10–12]. Understanding the factors associated with treatment outcomes is essential for informing targeted interventions and evidence-based policy development within the National Tuberculosis Program. Although several studies in Botswana have assessed TB treatment outcomes [13–15], treatment outcomes among individuals with RR-TB are understudied. Therefore, the study aim to evaluate the treatment outcomes among individuals diagnosed with RR-TB in Botswana and further identify predictors associated with unfavourable outcomes.

Materials and methods

Study setting

This study employed a retrospective cohort design to evaluate treatment outcomes among individuals diagnosed with RR-TB in Botswana between January 1, 2016, and June 30, 2023. In this study, RR-TB refers to individuals with rifampicin monoresistant TB (RR-TB) and MDR-TB, as determined by initial routine GeneXpert MTB/RIF Ultra and pDST results.

Study population

The study population consisted of individuals with laboratory-confirmed RR-TB who were enrolled in treatment programs consistent with National TB Treatment guidelines [8] at the six designated drug-resistant TB treatment clinics in Botswana. Diagnosis of RR-TB was established using routine molecular assays (GeneXpert MTB/RIF Ultra and Hain MTBDRplus) and phenotypic drug susceptibility testing (pDST) performed by the National Tuberculosis Reference Laboratory.

Inclusion and exclusion criteria

Eligible participants were individuals previously diagnosed with RR-TB, aged 18 years or older, with complete treatment records, including a documented treatment outcome. The primary outcome was favourable outcomes (cured) versus unfavourable outcomes (treatment failure, loss to follow-up [LFU], or death).

DNA extraction, whole genome sequencing and bioinformatics analyses

All samples previously diagnosed with RR-TB using GeneXpert MTB/RIF Ultra were genotyped by next-generation sequencing. DNA extraction, whole-genome sequencing, and bioinformatic analyses were performed retrospectively as previously described [16, 17]. Drug resistance genotypes for both first- and second-line antibiotics and lineages were inferred using TB-Profiler software, version 4.4.2 [18, 19].

Data collection and variables collected

Data were retrospectively extracted from national and district TB surveillance databases, including demographic characteristics, clinical history, microbiological test results, and treatment outcomes. The following variables: treatment outcome, TB treatment history, sex, HIV status, smear results, health district, and *Mycobacterium tuberculosis* (*M.tb)* lineages were extracted from the National TB Treatment database. Data were anonymised and cleaned before analysis to ensure completeness and consistency.

Treatment outcomes were assigned based on documented patient progress, in accordance with the WHO guidelines [20]. The treatment outcomes include cured, treatment failure, died, and LFU. Definitions are presented below in Table 1:

Statistical analysis

Baseline demographics were summarised as frequencies and percentages for categorical variables (with 95 % confidence intervals, [CI]) and as medians with interquartile ranges (IQR) for continuous variables. The proportions of treatment outcomes were estimated with 95 % CIs using the exact binomial method. Predictive factors associated with unfavourable treatment outcomes were assessed using a univariate logistic regression (Firth's logistic regression model). Firth's logistic regression model was used to reduce bias in maximum likelihood estimates of the coefficients [21]. The use of

Table 1
TB treatment outcomes and definitions.

Treatment outcome	Definition
Cured	A pulmonary TB patient with bacteriologically confirmed TB at the beginning of treatment who completed treatment as recommended by the national policy with evidence of bacteriological response and no evidence of failure.
Died	A patient who died before starting treatment or during the course of treatment.
Treatment failure:	A patient whose treatment regimen needed to be terminated or permanently changed to a new regimen or treatment strategy.
LFU	A TB patient who did not start treatment or whose treatment was interrupted for two consecutive months or more.

In this study, unfavourable treatment outcomes included LFU, treatment failure, and death, while favourable outcomes included cure. Individuals who were still on treatment or whose treatment outcome was unknown were excluded from the analyses.

Firth's logistic model helps reduce bias when there is a strong imbalance in the outcome, as is the case with our outcome variable. The variables evaluated were age, sex, HIV status, site of TB disease, previous treatment history, and *M.tb* lineage; p-values less than 0.05 indicated statistical significance. All statistical analyses were performed in STATA version 18 (Stata Corp, College Station, TX, USA) [22].

Results

Patient characteristics

A total of 202 individuals diagnosed with RR-TB were identified in Botswana between 1 January 2016 and 30 June 2023 and all were initiated on treatment. Of these, 40 individuals were excluded from analyses because they did not meet the study inclusion criteria: 36 had no documented treatment outcomes, and 4 were still receiving treatment at the time of analysis (Fig. 1). The final cohort, therefore, comprised 162 individuals with documented treatment outcomes. Of these, 102 (63 %) were male with a median age of 39 (IQR, 29–50). Nearly half of the individuals were from the Greater Gaborone health district 78/162 (48.1 %) (Fig. 2). In addition, 88/162 (54.3 %) were people living with HIV (PLWH), while one individual (0.6 %) had an unknown HIV status. All individuals with a confirmed HIV diagnosis at the time of TB diagnosis were initiated on antiretroviral treatment (ART) and cotrimoxazole preventive therapy (CPT). Most individuals were newly diagnosed with RR-TB [(121/162); 74.7 %] (Table 2).

Treatment outcomes

Among the 162 individuals with documented TB treatment outcomes, 137 (84.6 %) were cured, 18 (11.1 %) died during treatment, while 2 (1.2 %) had treatment failure. Additionally, five individuals (3.1 %) were lost to follow-up (Table 3).

Treatment outcomes by HIV status

Among individuals who were cured, the proportion was slightly higher among PLWH (71.8 %) than among PNLWH (69.2 %). In contrast, mortality was higher among PLWH (10.7 %) compared with PNLWH (6.6 %; 95 % CI: 2.5–13.8). The proportion of individuals lost to follow-up was lower among PLWH (1.9 %) than among PNLWH (2.2 %). Treatment failure was observed in 2.2 % of PNLWH (Supplementary Figure 1).

Factors associated with unfavourable outcomes

Males were 1.70 times more likely to experience unfavourable treatment outcomes than females, although this was not statistically significant. Similarly, individuals with a history of prior TB treatment had increased odds of unfavourable outcomes (OR = 1.03; 95 % CI: 0.40–2.73). Overall, none of the evaluated factors showed statistically significant associations with unfavourable treatment outcomes (Table 4).

Discussion

This study assessed the impact of clinical and demographic factors on TB treatment outcomes among individuals with RR-TB and demonstrated a treatment success rate of 84.6 %. The high treatment success rate suggests that the treatment approach implemented in this cohort was effective. Our findings are consistent with previous reports [23–26] and exceed the global RR-TB treatment success rate reported to the WHO [1]. The high success rate observed may reflect partly the improvements in TB diagnostic capacity and programmatic interventions,

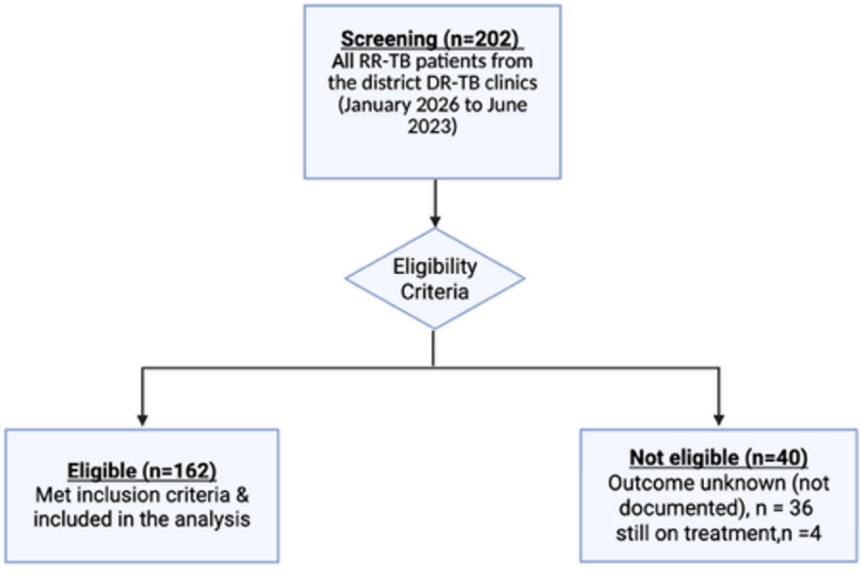

Fig. 1. Participant identification and inclusion criteria.

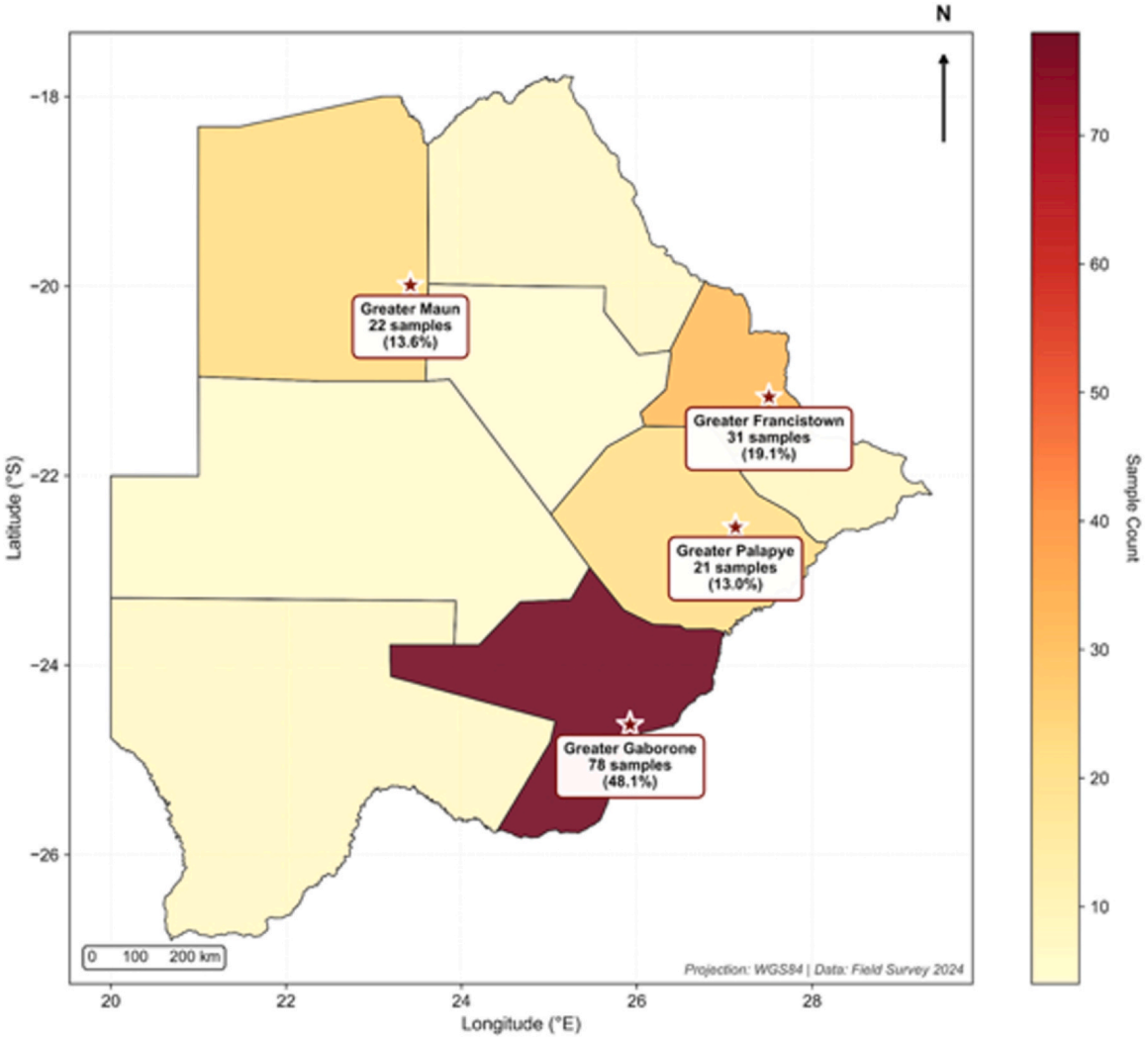

Fig. 2. Geographical distribution of individuals with RR-TB in Botswana.

including direct-observed therapy (DOTS) and the widespread use of rapid molecular diagnostic tools such as the Cepheid GeneXpert MTB/RIF Ultra system and line probe assays [27]. These tools facilitate earlier detection of rifampicin resistance, enabling timely initiation of appropriate treatment. However, subsequent WGS of isolates led to re-classification of some cases as MDR-TB or pre-XDR-TB. In routine programmatic settings where treatment decisions rely largely on GeneXpert and LPAs, individuals with undetected MDR or pre-XDR-TB may receive suboptimal regimens, which can compromise outcomes and reduce overall treatment success. This heterogeneity reflects real-world clinical practice and highlights the need to strengthen existing molecular diagnostics and expand access to pDST, while deploying genomic tools strategically. In resource-limited settings, targeted sequencing through referral of selected isolates to reference laboratories may be most feasible, particularly in cases of discordant results or suspected outbreaks.

Botswana's advances in HIV testing coverage and expanded ART access may also have contributed to the favourable outcomes observed among PLWH [23]. In this cohort, treatment success among PLWH was comparable to that observed among PNLWH, consistent with findings from other settings [28,29]. These results support the importance of maintaining integrated TB/HIV services to enable early diagnosis, prompt treatment initiation and continuity of care, which remain central to efforts to eliminate TB as a public health threat by 2030.

Despite the overall high treatment success rate, deaths comprised a notable proportion (> 10 %) of unfavourable outcomes, highlighting the need for strengthened patient monitoring, targeted adherence and clinical support. The higher rates of unfavourable outcomes in Zimbabwe and Colombia [12,30] compared to this study may reflect country-specific factors, including health-system capacity, treatment strategies and socioeconomic conditions that influence retention in care and survival.

Our study reported that nearly three-quarters of individuals with rifampicin resistance with no history of prior TB treatment. Rifampicin resistance is mostly reported among individuals with history of prior TB treatment(refs) The presence of rifampicin resistance at no prior TB treatment may suggest the potential ongoing transmission of existing resistant strains in Botswana [31,32]. The similar finding was observed in other high-burden settings where WGS has demonstrated that a substantial proportion of drug-resistant TB cases arise from transmission rather than inadequate treatment [33–35]. These findings highlight the urgent need to strengthen active case finding, contact tracing and infection prevention and control measures to interrupt transmission and limit further spread of rifampicin-resistant strains within the community [36].

Although unfavourable treatment outcomes occurred at a relatively low frequency, identifying predictors of these outcomes was

Table 2
Demographic and clinical characteristics of 162 individuals with rifampicin-resistant tuberculosis.

Characteristic	n	%
Sex (n = 162)		
Female	60	37.0
Male	102	63.0
Median Age in years (Q1, Q3) 39 (29,50)		
Health district		
Greater Gaborone	78	48.1
Greater Francistown	31	19.1
Greater Palapye	21	13.0
Greater Maun	22	13.6
Other*	10	6.2
HIV status		
Negative	73	45.1
Positive	88	54.3
Unknown	1	0.6
Smear results		
Negative	36	22.2
Positive	126	77.8
Site of TB disease		
Pulmonary	158	97.5
Extra-pulmonary	4	2.5
Previous treatment history		
New	121	74.7
Previously treated	41	25.3
M.tb lineages		
Lineage 4	98	60.5
Other lineages#	64	39.5
Genomic DR-TB type		
RR-TB	32	19.8
MDR-TB	99	61.1
Pre-XDR-TB	27	16.7
Sensitive	4	2.5

Other* included Ghanzi (n = 5), Kgalagadi (n = 4) and Boteti (n = 1) and health districts; observations less 10 per health district; HIV- Human immunodeficiency virus, other lineages# includes lineage 1 (n = 36), lineage 2 (n = 24), lineage 3 (n = 2) and mixed lineages (n = 2). All PLWH were on antiretroviral therapy.

Table 3
Tuberculosis treatment outcomes of 162 individuals based on WHO classification.

Treatment outcomes	n (Total =162)	% (95 % CI)
Favourable		
Cured	137	84.6 (78.1 – 89.8)
Unfavourable		
Died	18	11.1 (6.7 – 17.0)
Treatment failure	2	1.2 (0.1 – 4.4)
Lost to follow-up	5	3.1 (1.0 – 7.1)

challenging. None of the evaluated patient characteristics showed a significant association with unfavourable treatment outcomes. Being a male and aged below 39 years, had increased odds of treatment failure; however. Despite, we reported non-significant associations, some previous studies observed significant association between being a male and poorer treatment outcomes [37]. This difference may have been attributed by the modest sample size utilized. HIV status was not statistically associated with treatment success, although a higher mortality was observed among PLWH compared to PNLWH. This finding should be interpreted cautiously, as the study may have been underpowered to detect differences between subgroups, limiting the ability to draw definitive conclusions about their association.

Notably, several factors commonly linked to unfavourable outcomes, including socioeconomic and behavioural characteristics (such as educational attainment, employment status, smoking, alcohol use and other substance use) [8], could not be evaluated because they were not routinely captured or were insufficiently documented in the registers used for this retrospective analysis [9,29,38]. Lack of these variables may have resulted in residual confounding and reduced the ability to adjust for important predictors previously shown to influence treatment outcomes.

Improving outcome reporting in programmatic settings may also strengthen surveillance and patient monitoring. A previous study suggested that simplified WHO treatment outcomes definitions may better account for variation in sputum culture timing and conversion criteria in routine settings [39]. Simplified definitions were also reported to better identify individuals at higher risk of treatment failure compared with WHO-based criteria [39]. These findings highlight potential benefits of context-adapted outcome definitions to improve consistency and strengthen TB programme performance.

This study has several limitations that should be considered when interpreting the findings. First, the retrospective design and reliance on TB registers limited access to important clinical variables, including comorbidities (e.g., diabetes), immunological and virological markers among PLWH (e.g. CD4 and viral load), and other relevant indicators such as BMI. Secondly, the analysis may have been underpowered to detect statistically significant differences between subgroups. Many comparisons yielded broad and overlapping confidence intervals, increasing the likelihood of Type II error. Accordingly, the absence of statistically significant associations should not be interpreted as evidence of no effect, but rather as an indication that larger studies with richer datasets are required.

A further limitation was the lack of detailed information on treatment regimens, including drug dosing, treatment modifications,

Table 4
Predictive factors of unfavourable treatment outcomes (n = 162).

Variables	**Favourable (n = 137) n (%)**	**Unfavourable (n = 25) n (%)**	**p-values**	**Unadjusted Odds Ratio (95 % CI)**	**p-value**
Sex					0.21
Male	89 (65.0)	13 (52.0)	0.22	1.70 (0.73–3.98)	
Female	48 (35.0)	12 (48.0)		Ref	
Median Age in years (Q1, Q3)	39 (29, 50)	36 (29, 42)	0.51	1.0 (0.97–1.02)	0.67
HIV status					0.71
Positive	74 (54.0)	14 (56.0)	0.06	1.18 (0.50–2.79)	
Negative	63 (46)	10 (40.0)		Ref	
Site of infection					
Pulmonary	134 (97.8)	24 (96.0)	0.59	N/A	
Extrapulmonary	3 (2.2)	1 (4.0)		N/A	
TB treatment history					
New	102 (74.5)	19 (76)	0.87	Ref	
Previous treatment	35 (25.5)	6 (24)		1.03 (0.40–2.73)	0.94
***M.tb* Lineage**					0.73
Lineage 4	82 (59.9)	16 (64.0)	0.70	0.86 (0.40–2.04)	
Other*	55 (40.1)	9 (36)		Ref	

n represents the number of individuals in each treatment outcome category.
N/A: Not applicable, indicating that the odds ratio was not suitable for the respective variable.
* Other includes lineage 1, 2, 3 and other.

adverse events, adherence measures, and reasons for regimen changes. Some individuals may have received individualised regimens, and newer drugs such as bedaquiline could have influenced outcomes; however, these factors could not be assessed. The absence of regimen-level data limited the evaluation of regimen-specific effectiveness and may partly explain variability in outcomes. Future studies should incorporate detailed treatment histories and adherence measures to better characterise regimen-related determinants of treatment success.

We also acknowledge the exclusion of individuals without documented treatment outcomes. Forty individuals were excluded from the primary analysis to avoid misclassification; however, sensitivity analyses reclassifying these individuals as having unfavourable outcomes did not change the findings, with associations remaining non-significant. Nonetheless, residual bias cannot be fully excluded. Finally, diagnostic limitations may have affected resistance classification. Phenotypic DST for second-line drugs was not routinely available, and initial patient testing relied on Gene Xpert and LPA, which may miss non-canonical mutations and other complex resistance profiles [40]. Despite these limitations, the study provides valuable insights from real-world programmatic data and remains relevant for informing TB programme improvement in settings where comprehensive datasets are not routinely available.

Conclusion

In conclusion, the high treatment success rate of 84.6 % reflects a positive impact of improved diagnostics and treatment strategies in Botswana. Although no statistically significant associations were identified between clinical or demographic factors and unfavourable treatment outcomes, the higher mortality observed in PLWH may be clinically relevant. Enhanced patient monitoring and targeted interventions, particularly for vulnerable groups such as PLWH, remain essential to further improve treatment outcomes. Prospective studies with larger sample sizes and more comprehensive clinical, behavioural and socioeconomic data are warranted to validate these findings and better identify predictors of unfavourable treatment outcomes among individuals with RR-TB.

CRediT authorship contribution statement

Conceptualization: TM, RMW, EMS Methodology: EMS, RMW, AD, SM, TM, JHL, JTN Data curation and formal analysis: TM, OTC, JHL SM, EMS, JTN, PS Writing original draft: TM, SM, JTN Writing, review & editing: TM, OTC, EMS, RMW, AD, JHL, JTN, SG, SM, CM, OS, PS, TMM, KF, RMW, JM; Supervision: EMS, RMW, AD, SM, SG; Project administration: EMS, TM, SM, RMW; Funding acquisition: TM, SM, EMS. All authors read and approved the final manuscript.

Ethical approval

The study was approved by the Stellenbosch University Health Research Ethics Committee (HREC) [HREC Reference No: S22/12/271 (PhD)] and the Ministry of Health Human Research Development Division [Reference No: HPRD: 6/14/1]. Permission to use de-identified participant clinical information was granted; therefore, informed consent was waived. This study was conducted in accordance with the guidelines and regulations established by the ethics committees of the respective institutions and the Declaration of Helsinki.

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Data Availability

The original contributions presented in the study are publicly available. Sequencing data used in this study have been deposited in the European Nucleotide Archive (ENA) under project accession number PRJEB83872.

Declaration of Competing Interest

The authors declare that they have no known competing interests.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jiph.2026.103169.

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