Drug-Resistant Tuberculosis in Rural Eastern Cape: A Biosocial Pilot Study

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Article

Drug-Resistant Tuberculosis in Rural Eastern Cape: A Biosocial Pilot Study

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Abstract

Background: Drug-resistant tuberculosis (DR-TB) remains a major threat to global tuberculosis control, particularly in high-burden rural settings where transmission is driven by both biological and socio-structural determinants. Although genomic surveillance and mathematical transmission modelling have improved understanding of resistance evolution and transmission dynamics, these approaches often insufficiently incorporate community-level behavioral and social drivers of disease spread. This study integrated Community-Based Participatory Research (CBPR) within a genomic–epidemiological modelling framework to develop a biosocial understanding of DR-TB transmission dynamics in a rural South African setting. Methods: Whole-genome sequencing (WGS) was performed on 32 *Mycobacterium tuberculosis* isolates to identify resistance-associated mutations, phylogenetic lineages, and potential transmission clusters. A deterministic two-strain transmission model distinguishing drug-sensitive (DS) and drug-resistant (DR) tuberculosis was developed to simulate transmission dynamics. CBPR-informed mechanisms were incorporated into the model through modifications of key epidemiological parameters, including transmission rate (β), treatment initiation rate (γ), and resistance amplification rate (α), reflecting the influence of community engagement, treatment adherence, and health-seeking behavior. Scenario-based simulations evaluating varying levels of community-engaged interventions were conducted over a 10-year period. Results: A substantial burden of drug resistance was observed, with 84.4% of isolates resistant to at least one anti-tuberculosis drug. Multidrug-resistant tuberculosis (MDR-TB) accounted for 46.9% of isolates, while recurrent combinations of resistance-associated mutations suggested ongoing transmission of resistant strain lineages. Lineage 2 (Beijing genotype) and Lineage 4 predominated, with advanced resistance patterns occurring mainly within Lineage 2 isolates. Model simulations indicated that CBPR-informed interventions could reduce DS-TB transmission by approximately 40–60% and DR-TB transmission by 20–35%. Scenario-based estimates also indicated a higher transmission potential for DR-TB ($R_0 \approx 2.04$) than for DS-TB ($R_0 \approx 1.29$). Community-engaged interventions reduced transmission by improving treatment adherence, earlier diagnosis, and enhanced infection-prevention behaviors. Conclusions: Integrating CBPR into genomic and transmission modelling frameworks provides a novel biosocial approach for understanding tuberculosis dynamics in high-burden settings. The findings suggest that community-engaged interventions can substantially influence key epidemiological drivers of transmission and resistance amplification. Embedding community participation within TB surveillance and control strategies may strengthen efforts to reduce transmission, improve treatment continuity, and address the social determinants underpinning DR-TB persistence in rural settings.

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1. Introduction

Tuberculosis (TB), caused by *Mycobacterium tuberculosis* (Mtb), remains one of the leading global public health challenges, particularly in high-burden and resource-limited settings [1]. TB is broadly classified according to disease activity, anatomical site of infection, and drug-resistance profile. The disease exists in two principal forms: latent tuberculosis infection (LTBI), in which the bacteria remain inactive and asymptomatic, and active TB disease, which is symptomatic and transmissible, especially when pulmonary involvement is present [2]. In addition to pulmonary TB, extrapulmonary TB affects organs such as lymph nodes, bones, and the central nervous system, including the brain [3]. Despite major advances in TB diagnostics and treatment, the epidemic continues to threaten progress toward the World Health Organization End TB Strategy, underscoring the need for a deeper understanding of transmission dynamics, resistance evolution, and strain diversity [4]. Molecular characterization has become an essential approach for investigating TB transmission and resistance patterns by enabling detailed analysis of the genetic composition of Mtb strains. This process involves identifying genetic variations to determine strain diversity, evolutionary relationships, and transmission pathways. Conventional genotyping methods, including spoligotyping and MIRU-VNTR analysis, have historically been used to classify Mtb strains into distinct phylogenetic lineages. However, these approaches often lack sufficient discriminatory power to differentiate closely related strains, particularly in high-transmission settings [5]. Whole-genome sequencing (WGS) has substantially transformed TB molecular epidemiology by providing high-resolution genomic data through the identification of single-nucleotide polymorphisms (SNPs) across the Mtb genome. This allows precise strain differentiation, detection of transmission clusters, and identification of recent transmission events characterised by minimal genetic distances between isolates [8].

Tuberculosis may also be classified according to treatment response as either drug-sensitive TB (DS-TB) or drug-resistant TB (DR-TB). Drug-resistant forms include mono-resistant TB (resistance to a single first-line anti-TB drug), poly-resistant TB (resistance to more than one first-line drug excluding concurrent resistance to isoniazid and rifampicin), rifampicin-resistant TB (RR-TB), multidrug-resistant TB (MDR-TB), pre-extensively drug-resistant TB (pre-XDR-TB), and extensively drug-resistant TB (XDR-TB) [6]. Clinically, TB may further be categorised as primary TB, secondary or reactivation TB, and disseminated or miliary TB, in which infection spreads throughout the body [7]. The emergence and spread of DR-TB, particularly MDR-TB and XDR-TB, represent major obstacles to global TB control due to prolonged treatment duration, poorer treatment outcomes, and increased mortality [2].

Understanding TB transmission dynamics is essential for improving disease control strategies in endemic regions. Molecular epidemiology, particularly when integrated with epidemiological and clinical data, provides critical insights into transmission patterns, disease severity, and treatment outcomes [9]. Furthermore, WGS enables rapid identification of mutations associated with drug resistance, offering significant advantages over conventional phenotypic drug susceptibility testing. This is especially important in MDR-TB and XDR-TB, where early detection and timely initiation of effective treatment are crucial for improving patient outcomes and limiting ongoing transmission [2]. Drug resistance in *Mycobacterium tuberculosis* evolves primarily through the stepwise accumulation of mutations associated with resistance to first- and second-line anti-tuberculosis drugs. Key mutations in genes such as *rpoB*, *katG*, *fabG1*, *gyrA*, and *rrs* are linked to resistance against rifampicin, isoniazid, fluoroquinolones, and second-line injectable agents [10]. Understanding the distribution and co-occurrence of these mutations provides important insight into the evolutionary pathways leading from DS-TB to MDR-TB and XDR-TB [11].

In TB-endemic settings, transmission dynamics are shaped not only by biological factors but also by socioeconomic, environmental, and structural determinants. Integrating molecular

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characterisation with epidemiological data helps distinguish recent transmission from reactivation of latent infection and supports targeted public health interventions [12]. Recent studies increasingly highlight the role of genetic epidemiology in TB surveillance, outbreak investigation, and policy development, particularly in high-burden regions [13]. Consequently, WGS has become an increasingly important component of TB control efforts aimed at improving understanding of transmission networks and informing more effective intervention strategies.

Globally, TB transmission is strongly associated with several major phylogenetic lineages, particularly Lineage 2 (East Asian/Beijing genotype), Lineage 3 (Central Asian Strain [CAS]/Delhi lineage), and Lineage 4 (Euro-American lineage, including Latin American-Mediterranean [LAM], Haarlem, T, and X sublineages) [14]. Among these, Lineage 2, especially the Beijing genotype, is strongly associated with increased transmissibility, virulence, and a higher propensity for developing MDR-TB and XDR-TB. Genomic studies have shown that Beijing strains frequently demonstrate high clustering rates, suggesting ongoing transmission rather than independent acquisition of resistance, together with enhanced fitness under antibiotic pressure [15]. Similarly, Lineage 4 contributes substantially to the global burden of DR-TB, particularly in Southern and Eastern Africa, although it generally exhibits lower transmissibility compared with Beijing strains [15].

The distribution of TB genotypes reflects both historical and ongoing transmission dynamics, with modern lineages (Lineages 2–4) predominating in many high-burden African settings. The Beijing genotype has emerged as a major driver of MDR-TB and XDR-TB globally, while LAM and Haarlem strains also contribute significantly to drug resistance in Southern and Eastern Africa. In contrast, Lineages 5 and 6 (*Mycobacterium africanum*), which are largely confined to West Africa, are generally associated with lower transmissibility and lower resistance rates [16]. Importantly, molecular epidemiological studies across Africa have reported high levels of strain clustering among DR-TB isolates, suggesting that recent transmission, rather than de novo resistance emergence, is a major contributor to the DR-TB epidemic.

South Africa remains among the countries with the highest TB burden globally and provides strong evidence of genotype-driven transmission dynamics. The Beijing genotype is widely distributed and strongly associated with RR-TB, MDR-TB, and XDR-TB, particularly in the Western Cape and Eastern Cape provinces [17]. In addition, specific Lineage 4 sublineages, such as the F15/LAM4/KZN strain, have been linked to major XDR-TB outbreaks and sustained community transmission. WGS studies conducted in South Africa suggest that transmission of already resistant strains is a major driver of the epidemic, with extensive genomic clustering observed among MDR-TB and XDR-TB isolates [18]. The Eastern Cape, together with KwaZulu-Natal, remains among the provinces with the highest DR-TB burden, including reports of totally drug-resistant TB (TDR-TB) [18]. More recently, transmission-driven resistance to newer anti-TB drugs such as bedaquiline has been reported, highlighting the growing threat posed by highly transmissible drug-resistant Mtb strains [19]. Identification of high-risk lineages and mapping of transmission networks are therefore essential for informing targeted interventions, optimizing treatment strategies, and strengthening TB control programmes.

The molecular epidemiology of *Mycobacterium tuberculosis* has important public health implications, particularly in high-burden settings where specific genotypes drive both transmission and drug resistance. The prevalence of high-risk lineages such as Beijing (Lineage 2) and LAM (Lineage 4), both strongly associated with MDR-TB and XDR-TB, underscores the importance of integrating molecular surveillance approaches such as WGS into routine TB control programmes [20]. High levels of genomic clustering among DR-TB isolates indicate that ongoing transmission, rather than independent resistance emergence, is a major contributor to the epidemic. This highlights the need for strengthened infection prevention and control measures, enhanced contact tracing, and targeted interventions in transmission hotspots. Advances in WGS have substantially improved understanding of TB transmission through precise identification of resistance-associated mutations, phylogenetic classification, and detection of genomic clusters associated with ongoing transmission [21]. In parallel, mathematical transmission models provide robust frameworks for simulating

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epidemic trajectories and evaluating the impact of interventions [22]. These models are increasingly used to estimate the relative contributions of recent transmission versus reactivation and to assess the population-level effects of diagnostic and treatment strategies. However, TB transmission is not driven solely by biological factors. It is also profoundly shaped by social and structural determinants including delayed healthcare-seeking behaviour, stigma, poverty, and limited access to healthcare services [23]. These challenges are especially pronounced in rural South African settings, where substantial gaps in screening, diagnosis, and treatment persist despite technological advances.

Community-Based Participatory Research (CBPR) offers an important framework for addressing these limitations by actively involving communities in the co-production of knowledge and intervention strategies. Through fostering trust, contextual relevance, and local ownership, CBPR can enhance both the effectiveness and sustainability of public health interventions [24]. Despite its recognized importance, CBPR has rarely been explicitly integrated into genomic surveillance and transmission modelling frameworks. This study addresses this gap by combining genomic surveillance, mathematical modelling, and CBPR to develop a comprehensive biosocial understanding of DR-TB transmission dynamics in a rural South African setting. By integrating genotype-informed strategies with community-driven interventions, this approach has the potential to improve early diagnosis, guide targeted resource allocation, and strengthen efforts to interrupt transmission and reduce the burden of drug-resistant tuberculosis in endemic communities.

2. Methodology

2.1. Study Design

This study employed an integrated genomic–epidemiological modelling framework to investigate the transmission dynamics of drug-sensitive (DS) and drug-resistant (DR) tuberculosis (TB) in a high-burden rural setting. The study combined whole-genome sequencing (WGS) analysis of *Mycobacterium tuberculosis* isolates with deterministic mathematical transmission modelling to provide a comprehensive understanding of resistance evolution, strain diversity, and transmission dynamics. The integrated design was selected to address important limitations in conventional TB research approaches, which frequently examine biological, epidemiological, or social determinants of transmission in isolation rather than as interconnected processes.

Whole-genome sequencing was used to identify resistance-associated mutations, characterise phylogenetic lineage diversity, and infer potential transmission clusters among circulating *M. tuberculosis* strains. These genomic findings informed the parameterisation of a deterministic two-strain transmission model distinguishing DS-TB from DR-TB. The model was structured to capture key epidemiological and programmatic processes influencing TB transmission, including:

- infection;
- latent disease progression;
- treatment initiation;
- treatment response and recovery; and
- the emergence and amplification of drug resistance during treatment.

The modelling framework incorporated separate transmission pathways for DS-TB and DR-TB to account for differences in transmissibility, treatment outcomes, and resistance evolution. This enabled simulation of both biological transmission processes and health system–related factors influencing TB dynamics within the study population.

To strengthen the biosocial relevance of the model, Community-Based Participatory Research (CBPR)-informed mechanisms were integrated into the analytical framework. Rather than functioning solely as a qualitative component, CBPR principles informed modifications of key epidemiological parameters to reflect the influence of community-level social and behavioural determinants on TB transmission. Specifically, the model incorporated adjustments to:

- transmission rate (β);
- treatment initiation rate (γ); and

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- resistance amplification rate (α).

These parameter modifications were designed to reflect the potential effects of:

- health-seeking behaviour;
- treatment adherence;
- healthcare accessibility;
- community trust;
- stigma reduction;
- and continuity of care.

Scenario-based simulations were conducted over a 10-year time horizon to evaluate the potential impact of varying levels of community-engaged interventions on the transmission dynamics of both DS-TB and DR-TB. Intervention scenarios examined the possible effects of improved health literacy, earlier healthcare utilisation, enhanced adherence support, and strengthened community participation on transmission reduction and resistance amplification. The modelling approach therefore enabled simultaneous assessment of biological, epidemiological, and social determinants of TB transmission within a unified framework.

The integration of genomic epidemiology, mathematical modelling, and CBPR represents a novel biosocial approach to understanding DR-TB transmission in resource-limited settings. By embedding community-informed mechanisms within the transmission model, the study aimed to move beyond purely biomedical representations of TB transmission and incorporate broader structural and behavioural influences shaping disease dynamics in real-world settings.

Several methodological limitations should, however, be acknowledged. First, the genomic component was based on a relatively small cross-sectional sample of isolates, which limited the ability to fully capture temporal transmission dynamics and within-host genomic evolution. Second, the deterministic model structure simplified complex transmission processes and could not fully account for stochastic variation, heterogeneous mixing patterns, migration, or changing healthcare system conditions over time. Third, CBPR-informed parameter modifications were conceptual and scenario-based rather than empirically estimated from longitudinal intervention data. Consequently, the findings should be interpreted as exploratory and hypothesis-generating rather than predictive or causal. Despite these limitations, the integrated framework provides an important proof-of-concept model for incorporating biosocial determinants into genomic and transmission modelling approaches for tuberculosis control in high-burden settings.

2.2. Whole-Genome Sequencing Analysis

Whole-genome sequencing (WGS) was performed on 32 Mycobacterium tuberculosis clinical isolates to enable high-resolution characterisation of genomic variation associated with drug resistance, phylogenetic lineage diversity, and transmission dynamics. WGS was selected because of its superior discriminatory power compared with conventional genotyping approaches and its ability to simultaneously identify resistance-associated mutations, infer phylogenetic relationships, and detect potential transmission clusters at high genomic resolution.

Genomic DNA extraction and library preparation were performed using standardised laboratory protocols. DNA was fragmented enzymatically using the NEB Ultra II FS kit, followed by fragment size selection (200–700 bp) using AMPure XP beads. Fragmented DNA underwent end repair and ligation with Illumina-specific adapter sequences. Each sample was individually indexed to enable multiplex sequencing, followed by a second size-selection step to optimise library quality. Libraries were quantified using fluorometric methods, normalised to a concentration of 4 nM, and sequenced on the Illumina MiSeq platform using the MiSeq v3 600-cycle kit according to the manufacturer's standard protocol. Approximately 220 Mb of paired-end sequencing data (2 × 300 bp reads) were generated per isolate, providing sufficient genomic coverage for high-confidence variant detection and lineage classification. Raw sequencing reads underwent quality control and preprocessing using validated bioinformatics pipelines. Initial resistance profiling and phylogenetic lineage classification were performed using TB-Profiler (https://github.com/jodyphelan/TBProfiler),

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which aligns sequencing reads against the M. tuberculosis H37Rv reference genome and identifies strain-specific sequence variants associated with lineage assignment and anti-tuberculosis drug resistance [25]. Resistance inference was based on a curated database of validated resistance-associated mutations integrated within the TB-Profiler framework. To strengthen analytical robustness and improve variant confidence, raw WGS data were additionally processed using the USAP pipeline. Sequencing reads were quality-trimmed using Trimmomatic [26] with a sliding-window approach and a minimum average Phred quality score threshold of 20. High-quality reads were aligned to the M. tuberculosis H37Rv reference genome (GenBank accession NC000962.3) using multiple alignment algorithms, including:

BWA [27];

SMALT [28]; and

Novoalign (Novocraft). Genomic variants, including single-nucleotide variants (SNVs) and small insertions/deletions (1–10 base pairs), were identified using SAMtools [29] and the Genome Analysis Toolkit (GATK) [30]. To minimise false-positive variant calls and improve analytical reliability, only variants consistently identified across all alignment approaches were retained for downstream analysis. This conservative multi-aligner strategy enhanced confidence in mutation detection and resistance inference. Targeted genomic analysis focused on well-characterised resistance-associated loci implicated in resistance to first- and second-line anti-tuberculosis drugs, including:

rpoB (rifampicin resistance);

katG and the fabG1 promoter region (isoniazid resistance);

gyrA (fluoroquinolone resistance); and

rrs (second-line injectable resistance).

Detected mutations within these loci were used to infer resistance phenotypes and classify isolates into clinically relevant resistance categories:

drug-sensitive TB;

non-MDR drug-resistant TB;

multidrug-resistant TB (MDR-TB);

pre-extensively drug-resistant TB (pre-XDR-TB); and

extensively drug-resistant TB (XDR-TB).

This classification framework enabled structured assessment of resistance severity, resistance progression pathways, and the accumulation of resistance-associated mutations across circulating strains. Phylogenetic lineage classification was conducted to characterise strain diversity and assess lineage distribution within the study population. Comparative genomic analysis was subsequently used to evaluate genetic relatedness among isolates and identify potential transmission clusters based on shared mutation profiles and minimal genomic variation. Pairwise genetic distances were initially assessed using a threshold of ≤10 single-nucleotide polymorphisms (SNPs), consistent with molecular epidemiological approaches used to infer genetic relatedness among circulating strains. Genomic transmission clusters suggestive of recent transmission were subsequently defined using a more stringent ≤5 SNP threshold, in accordance with established criteria for recent transmission in M. tuberculosis molecular epidemiology. Clustered isolates sharing highly similar genomic profiles and resistance-associated mutations were interpreted as suggestive of recent or ongoing transmission rather than independent de novo emergence of resistance. However, clustering analyses were interpreted cautiously because genomic similarity alone cannot definitively establish direct person-to-person transmission in the absence of supporting epidemiological linkage data such as contact tracing, temporal information, or geographic proximity. Consequently, identified genomic clusters were considered indicative of potential transmission networks requiring further epidemiological investigation. Several methodological limitations should be acknowledged. First, the relatively small number of isolates limited the ability to fully characterise population-level transmission dynamics and genomic diversity within the broader community. Second, the cross-sectional design precluded direct assessment of temporal transmission patterns and within-host evolutionary dynamics. Third,

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resistance inference was based on currently recognised resistance-associated mutations and may not fully capture novel or poorly characterised resistance mechanisms. Despite these limitations, the integration of high-resolution WGS with comparative genomic analysis provided important insight into resistance evolution, strain diversity, and transmission dynamics within a high-burden tuberculosis setting.

2.3. Identification of Potential Transmission Clusters

Comparative genomic analysis was conducted across all Mycobacterium tuberculosis isolates to identify shared combinations of resistance-associated mutations and assess potential transmission clustering within the study population. Mutation profiles, phylogenetic lineage assignments, and pairwise single-nucleotide polymorphism (SNP) distances were evaluated to determine genomic relatedness among isolates. Recurrent mutation signatures and highly similar genomic profiles were used as proxies for clustering and as indicators of possible transmission of drug-resistant strains within the study setting. Pairwise genetic relatedness between isolates was initially assessed using a ≤10 SNP threshold to identify genetically related strains, while potential recent transmission clusters were subsequently defined using a more stringent ≤5 SNP threshold, consistent with established molecular epidemiological criteria for recent M. tuberculosis transmission. Isolates sharing highly similar resistance-associated mutation patterns together with minimal genomic variation were interpreted as suggestive of recent or ongoing transmission events rather than independent de novo acquisition of resistance mutations. Although the dataset represented a cross-sectional genomic snapshot rather than a longitudinal transmission dataset, the presence of identical or near-identical genomic profiles across multiple isolates provided indirect evidence supporting clonal transmission of circulating drug-resistant strains. Comparative clustering analysis, therefore, enabled the identification of potential epidemiologically linked cases and offered insight into broader transmission dynamics operating within the study population. In addition to resistance-associated loci, overall genomic similarity and phylogenetic lineage concordance were considered during cluster interpretation to reduce the likelihood of falsely attributing unrelated strains to the same transmission network. Particular attention was given to clustering among isolates belonging to high-risk lineages previously associated with increased transmissibility and multidrug resistance, including Beijing (Lineage 2) and Lineage 4 sublineages. However, genomic clustering alone cannot definitively confirm direct person-to-person transmission, as genetically similar isolates may also reflect the circulation of endemic strain populations within high-burden settings. Furthermore, the absence of detailed epidemiological linkage data, including temporal information, geographic proximity, contact tracing, and patient social network data, limited the ability to confirm transmission directionality or transmission chains. Consequently, identified clusters were interpreted cautiously as putative transmission networks requiring further epidemiological validation. Despite these limitations, the integration of high-resolution WGS and comparative genomic analysis provided important insight into the possible contribution of ongoing transmission to the burden of drug-resistant tuberculosis within the study setting and strengthened understanding of the genomic epidemiology of circulating strains.

2.4. Transmission Model

A deterministic compartmental model was developed to simulate the transmission dynamics of drug-sensitive (DS) and drug-resistant (DR) tuberculosis within a structured population. The total population was stratified into epidemiological compartments representing:

- Susceptible individuals (S)
- Latent infection with DS and DR strains (E_s, E_r)
- Infectious disease with DS and DR strains (I_s, I_r)
- Individuals on treatment (T_s, T_r)
- Recovered individuals (R_s, R_r)

The total population was defined as:

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$$N = S + E_s + I_s + T_s + R_s + E_r + I_r + T_r + R_r$$

Separate transmission pathways were modelled for DS-TB and DR-TB to capture differences in transmissibility, treatment response, and resistance dynamics. Transmission occurred through effective contact between susceptible individuals and infectious cases, with distinct forces of infection governed by transmission rates (β_s for DS-TB and β_r for DR-TB).

Individuals progressed from latent infection to active disease at rates (σ_s, σ_r), initiated treatment at rates (γ_s, γ_r), and recovered at rates (ϱ_s, ϱ_r). The model also incorporated a resistance amplification parameter (α), representing the acquisition of drug resistance during treatment due to incomplete adherence, delayed diagnosis, or suboptimal therapeutic regimens. This mechanism allowed transitions from drug-sensitive to drug-resistant states within the treatment compartment. Key epidemiological parameters included transmission rates, progression rates, treatment initiation rates, recovery rates, and resistance amplification. Together, these parameters enabled simulation of both biological processes and programmatic factors influencing tuberculosis transmission dynamics.

2.5. Integration of CBPR

CBPR was incorporated as a guiding framework to integrate social and behavioral determinants into the transmission modelling approach. Rather than serving solely as a qualitative component, CBPR informed modifications to key epidemiological parameters to reflect real-world community dynamics.

The CBPR process involved the following core components:

- Partnership development and trust-building with community stakeholders
- Co-identification of barriers to TB prevention, diagnosis, and treatment
- Co-design of context-specific intervention strategies
- Collaborative interpretation of findings
- Action-oriented implementation and feedback

Insights derived from CBPR were translated into model adjustments by modifying key parameters:

- Reduction in transmission rates (β) through improved infection prevention behaviors and reduced exposure.
- Increase in treatment initiation rates (γ) driven by earlier care-seeking and improved access to services
- Reduction in resistance amplification (α) through enhanced treatment adherence and continuity of care

This integration enabled the model to reflect the influence of community engagement on transmission dynamics, thereby embedding a biosocial perspective into the analytical framework.

2.6. Simulation of Community-Engaged Health Literacy Interventions

To assess the potential impact of community-engaged TB health literacy interventions, scenario-based simulations were incorporated into the transmission model by systematically modifying key epidemiological parameters.

Specifically, the model accounted for:

- Reduced transmission rates (β_s, β_r), reflecting improved infection prevention practices and decreased exposure risk
- Increased treatment initiation rates (γ_s, γ_r), associated with enhanced symptom recognition and timely healthcare utilization
- Reduced resistance amplification (α), resulting from improved adherence, treatment completion, and retention in care

Three intervention scenarios were defined:

- Baseline scenario: No community-based intervention
- Moderate CBPR intervention: Partial improvements in health literacy, care-seeking behavior, and treatment adherence

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- High-intensity CBPR intervention: Substantial and sustained improvements driven by active community engagement and co-designed interventions

All simulations were conducted over a 10-year time horizon to evaluate the long-term effects of community-engaged health literacy interventions on TB transmission dynamics and the evolution of drug resistance. This approach enabled a comparative analysis of intervention effectiveness across varying levels of community engagement.

3. Results

3.1. Distribution of Drug-Sensitive and Drug-Resistant Strains

WGS analysis was performed on 32 Mycobacterium tuberculosis isolates to characterize resistance profiles and infer potential transmission dynamics. The dataset revealed a high burden of drug resistance, with 27 of 32 isolates (84.4%) showing resistance to at least one anti-tuberculosis drug. Only 5 isolates (15.6%) were fully drug sensitive.

Among resistant isolates, multidrug-resistant tuberculosis (MDR-TB) accounted for the largest proportion (46.9%, n = 15), followed by drug-resistant non-MDR strains (18.8%, n = 6). More advanced resistance categories were also identified, including pre-XDR TB (6.2%, n = 2) and XDR TB (9.4%, n = 3). One isolate (3.1%) was classified as pre-MDR. The presence of pre-XDR and XDR isolates indicates progression along the resistance continuum and suggests ongoing selective pressure within the local transmission network.

3.2. Lineage Distribution

Phylogenetic lineage assignment revealed that isolates were dominated by Lineage 4 (Euro-American lineage) and Lineage 2 (East Asian/Beijing lineage). Lineage 4 accounted for 46.9% (n = 15) of isolates, while lineage 2 represented 40.6% (n = 13). Only a small number of isolates belonged to Lineage 1 (n = 1) and Lineage 3 (n = 1), with one isolate displaying mixed lineage characteristics.

Notably, higher-order drug resistance (pre-XDR and XDR) occurred predominantly within Lineage 2, whereas MDR-TB isolates were distributed across both Lineage 2 and Lineage 4.

3.3. Resistance-Associated Mutations

Genotypic analysis identified several canonical mutations associated with resistance to first- and second-line anti-tuberculosis drugs.

Rifampicin resistance mutations (conferred by mutations in the rpoB gene resulting in high-level resistance) were detected in 26 isolates, with rpoB Ser450Leu representing the most common variant. Additional mutations were observed in other positions of the rpoB rifampicin resistance-determining region.

Isoniazid resistance mutations were (commonly associated with katG mutations leading to high level resistance while mutations in inhA promoter region causes low level resistance) present in 23 isolates, most commonly involving katG Ser315Thr and the fabG1 promoter mutation (−15C>T).

Fluoroquinolone resistance mutations were identified in five isolates, predominantly in gyrA codon 94 substitutions, consistent with pre-XDR and XDR phenotypes.

Resistance to second-line injectable agents was associated with mutations in the rrs gene (1401A>G) and was detected in eight isolates suggesting resistance to streptomycin.

Several isolates shared identical combinations of resistance mutations, suggesting the presence of genomic clusters consistent with possible clonal transmission rather than independent resistance emergence.

3.4. Evidence Suggestive of Resistant Strain Transmission

Repeated resistance signatures were observed across multiple isolates (Figure 1), particularly combinations involving rpoB Ser450Leu with fabG1 −15C>T or katG Ser315Thr. Such recurrent

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mutation patterns suggest that certain resistant strains may be circulating within the study population rather than arising solely from treatment failure.

Furthermore, clustering of advanced resistance within lineage 2 isolates supports the hypothesis that specific phylogenetic lineages may facilitate the transmission and persistence of highly resistant strains.

WGS analysis was conducted to explore resistance patterns, strain relationships, and potential transmission dynamics among Mycobacterium tuberculosis isolates. Mutation-based clustering, mutation co-occurrence analysis, and mathematical modeling were used to examine the relative contribution of DS and DR strains to transmission dynamics.

Hierarchical clustering of resistance mutation profiles identified several groups of closely related isolates. Shared combinations of canonical resistance mutations, including variants in rpoB, katG, fabG1, gyrA, and rrs characterize these clusters. The clustering pattern suggests that resistant strains may not arise independently in each patient but instead may reflect ongoing transmission of established resistant strain lineages.

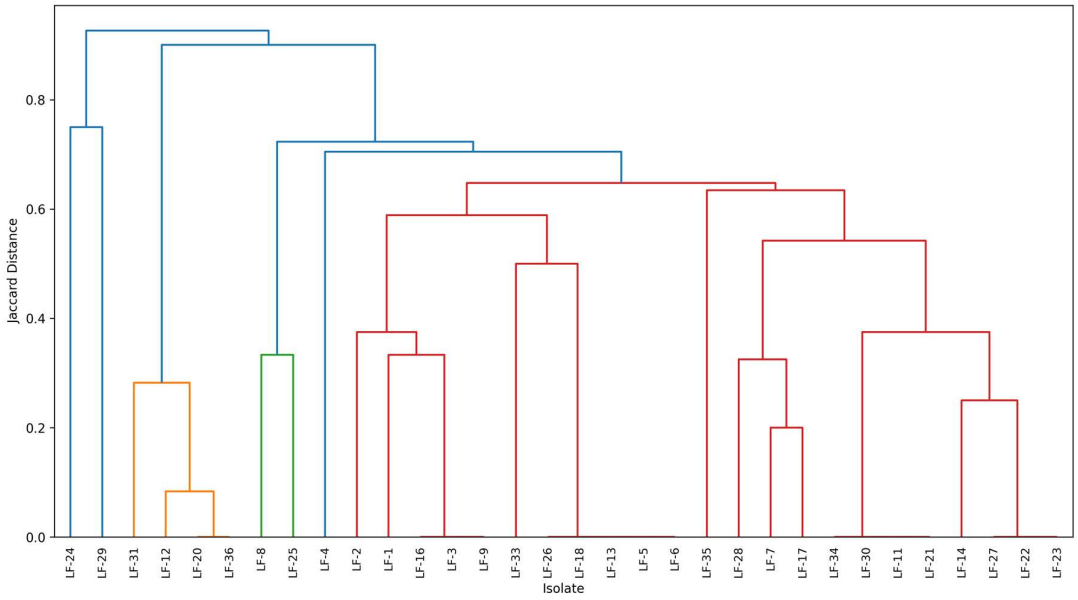

Figure 1. Transmission cluster dendrogram derived from WGS resistance mutation profiles. Hierarchical clustering based on shared resistance-associated mutations across isolates. The dendrogram illustrates similarity relationships between isolates (LFs) and identifies potential genomic clusters suggestive of transmission of related resistant strains.

3.5. Mathematical Model Framework for DS–DR TB Transmission

To investigate the transmission dynamics suggested by the genomic data (Figure 2), a two-strain tuberculosis transmission model distinguishing DS and DR strains can be formulated.

The population is divided into susceptible (S), latent infection (E), infectious disease (I), treatment (T), and recovered (R) compartments for both DS and DR tuberculosis strains. Transmission occurs through contact with infectious individuals with forces of infection. $\beta_s I_s/N$ and $\beta_r I_r/N$. Individuals progress from latent to active disease at rates. σ_s and σ_r, initiate treatment at rates γ_s and γ_r, and recover at rates ρ_s and ρ_r. DR may emerge through amplification during treatment of drug-sensitive infection (α) or through transmission of resistant strains.

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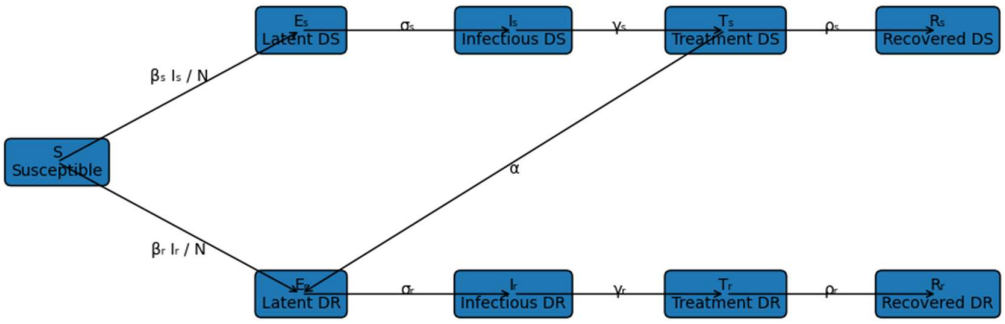

Figure 2. Two-strain transmission model for drug-sensitive and drug-resistant tuberculosis.

Population Compartments:

- S – Susceptible
- E_s – Latent drug-sensitive infection
- I_s – Infectious DS-TB
- T_s – Treatment for DS-TB
- R_s – Recovered DS-TB
- E_r – Latent drug-resistant infection
- I_r – Infectious DR-TB
- T_r – Treatment for DR-TB
- R_r – Recovered DR-TB

The population is divided into susceptible individuals (S), latent infection (E), infectious disease (I), treatment (T), and recovered (R) compartments for both drug-sensitive and drug-resistant TB strains.

Total population: $N = S + Es + Is + Ts + Rs + Er + Ir + Tr + Rr$

Transmission parameters shown

- $\beta_s I_s / N$ – force of infection for DS strain
- $\beta_r I_r / N$ – force of infection for DR strain
- σ_s, σ_r – progression from latent to active TB
- γ_s, γ_r – treatment initiation rates
- ϱ_s, ϱ_r – recovery rates
- α – resistance amplification during DS treatment

The model incorporates transmission of drug-sensitive TB, transmission of drug-resistant TB, progression from latent to active disease, treatment initiation and recovery, resistance amplification during treatment (parameter α), and TB-related mortality.

Integrated Genomics-to-Transmission Framework

WGS identifies recurrent resistance mutations (Figure 3) and mutation clusters across Mycobacterium tuberculosis isolates. Shared mutation signatures allow inference of potential transmission networks among resistant strains. These genomic insights inform a two-strain mathematical transmission model distinguishing DS and DR tuberculosis. Model simulations are then used to estimate epidemiological parameters and project the future burden of drug-resistant TB.

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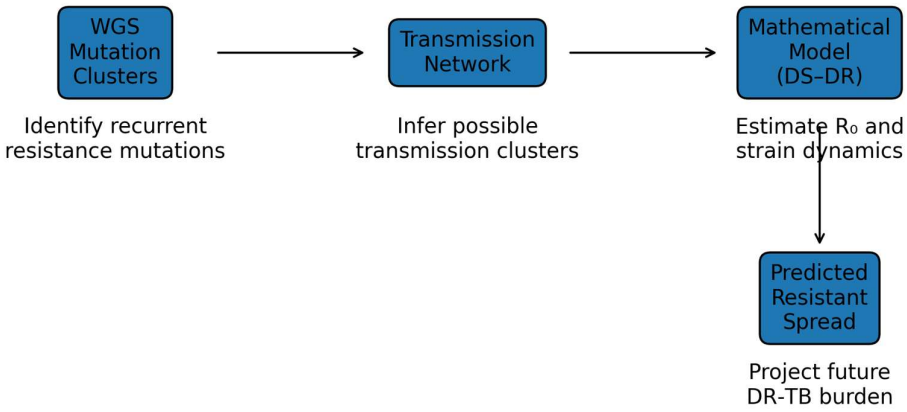

Figure 3. Integrated genomics-to-transmission framework for drug-resistant tuberculosis.

3.6. Resistance Evolution Pathway

The stepwise acquisition of resistance mutations (Figure 4) drives progression from drug-sensitive tuberculosis to MDR, pre-XDR, and XDR tuberculosis. MDR-TB typically arises through mutations conferring rifampicin and isoniazid resistance, commonly involving rpoB together with katG or the fabG1 promoter region. Additional mutations in gyrA confer resistance to fluoroquinolones, defining pre-XDR TB. Further mutations in the rrs gene confer resistance to second-line injectable agents, resulting in XDR TB.

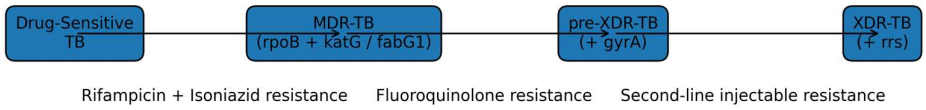

Figure 4. Evolutionary pathway of drug resistance in *Mycobacterium tuberculosis*.

Model-based estimation (Figure 5) of the basic reproduction number in Figure 6 suggested that drug-resistant TB may exhibit higher effective transmission potential than drug-sensitive TB in the modeled scenario ($R_0 \approx 2.04$ for DR-TB vs $R_0 \approx 1.29$ for DS-TB). Although these values represent scenario-based estimates rather than direct empirical measurements, they highlight how resistant strains can persist and spread within populations if they retain transmission fitness.

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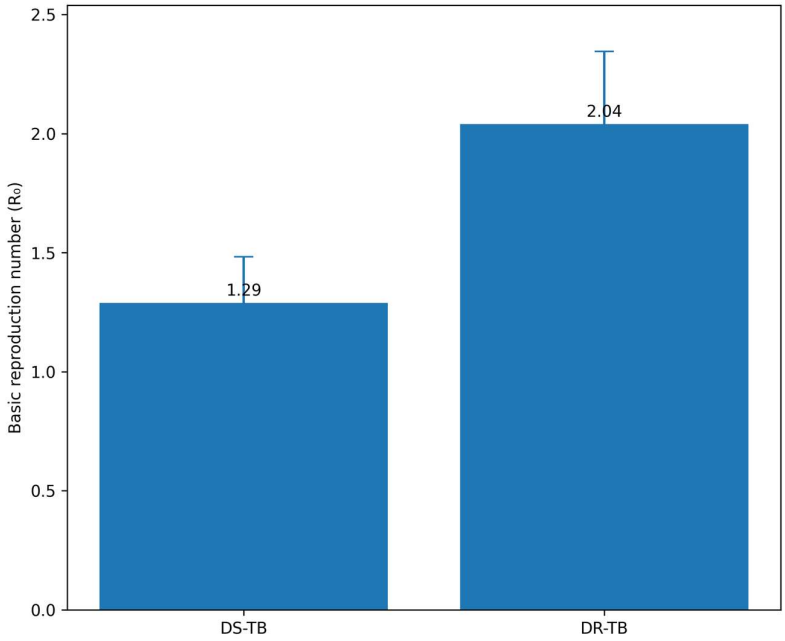

Figure 5. Scenario-based estimates of the basic reproduction number (R_0) for drug-sensitive and drug-resistant tuberculosis—model-derived R_0 estimates obtained from a two-strain compartmental TB transmission model. Error bars represent uncertainty ranges generated through parameter variation.

Simulation of future transmission trajectories (Figure 5) demonstrated that drug-resistant infections may remain dominant in the modeled population over time. While both DS and DR cases initially decline due to treatment dynamics, resistant infections show a gradual resurgence, suggesting that incomplete treatment success or ongoing transmission can sustain the circulation of resistant strains.

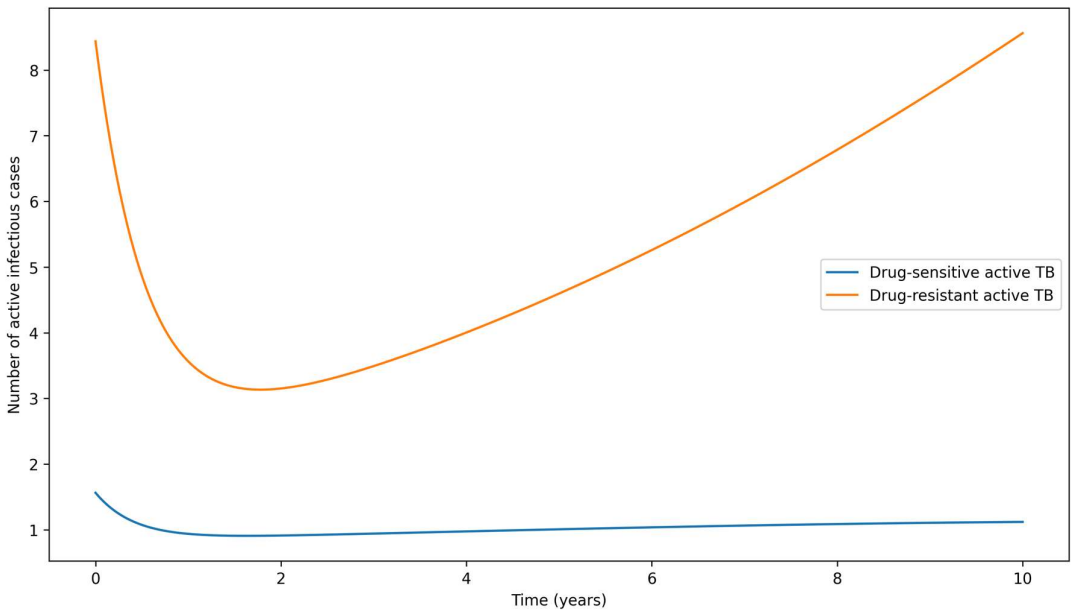

Figure 6. Simulated future trajectories of drug-sensitive and drug-resistant tuberculosis. Forward simulations from a two-strain compartmental model showing projected numbers of active drug-sensitive and drug-resistant infectious cases over ten years.

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3.7. Modeling the Impact of Community-Engaged TB Health Literacy on Transmission

Social and behavioral determinants, including delayed care-seeking, incomplete treatment adherence, stigma, and limited knowledge about transmission pathways, strongly influence tuberculosis transmission. Community-engaged education programs that improve TB health literacy can influence several key epidemiological parameters within transmission models.

In the DS–DR transmission framework developed in this study, community-engaged TB health literacy interventions are expected to influence three major mechanisms:

- Earlier diagnosis and treatment initiation
- Improved treatment adherence
- Reduced transmission through behavioral awareness

These mechanisms collectively reduce the effective reproduction number (R_e) and interrupt transmission chains.

3.8. Parameter Pathways Affected by Health Literacy

Within the model, the following parameters are most sensitive to community education interventions:

1. Reduced Transmission Rate

Health literacy interventions increase community awareness of key infection prevention practices, including cough etiquette, improved ventilation, early symptom recognition, and household-level infection control. These behavioral changes reduce the probability of effective contact between infectious and susceptible individuals. Within the model, this effect is represented as a proportional reduction in the transmission coefficients for both drug-sensitive and drug-resistant strains, such that $\beta_s \rightarrow \beta_s(1-\varepsilon)$ and $\beta_r \rightarrow \beta_r(1-\varepsilon)$, where ε denotes the effectiveness of community education in reducing transmission. Consistent with evidence from modeling studies, strong community-based education programs are typically associated with a 10–40% reduction in effective contact rates, reflecting meaningful declines in transmission intensity at the population level.

2. Faster Treatment Initiation

Community education improves recognition of TB symptoms, increases willingness to seek healthcare, and reduces stigma associated with the disease. These changes enhance timely health-seeking behavior, thereby increasing the treatment initiation rates for both drug-sensitive and drug-resistant tuberculosis (γ_s and γ_r). As a result, the duration of infectiousness is shortened. Within the transmission framework, this has a direct epidemiological impact, as the basic reproduction number (R_0) is inversely related to the rate of treatment initiation ($R_0 \propto 1/(\gamma + \mu + d)$). Consequently, increases in γ substantially reduce R_0, contributing to the interruption of transmission and improved population-level control of tuberculosis.

3. Reduced Resistance Amplification

Improved health literacy also strengthens treatment adherence, enhances patient understanding of treatment duration, and reduces the likelihood of treatment interruption. These factors collectively improve treatment continuity and effectiveness. Within the model, this is represented by a reduction in the resistance amplification parameter (α), indicating a lower probability that drug-sensitive infections will progress to drug-resistant forms during treatment. Consequently, improved adherence driven by community education helps limit the emergence and spread of drug-resistant tuberculosis.

3.9. Predicted Epidemiological Impact

Using the DS–DR model developed earlier, integrating health literacy into the system produces several predicted outcomes.

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3.9.1. Reduction in Basic Reproduction Number

Under the previously estimated baseline scenario, the basic reproduction number (R_0) was approximately 1.29 for drug-sensitive TB (DS-TB) and 2.04 for drug-resistant TB (DR-TB), indicating sustained transmission in both groups. Incorporating community-engaged health education resulting in a 25% reduction in transmission leads to a marked decline in these values, with DS-TB decreasing to approximately 0.97 and DR-TB to 1.53. This shift suggests that transmission of drug-sensitive TB could fall below the epidemic threshold ($R_0 < 1$), indicating potential interruption of sustained spread. In contrast, drug-resistant TB transmission, although reduced, remains above the threshold and therefore continues to pose a public health risk requiring targeted interventions.

3.9.2. Shorter Infectious Period

Community health literacy interventions reduce delays between symptom onset and diagnosis by improving symptom recognition and promoting timely healthcare-seeking behavior. In the baseline scenario, the time to treatment initiation is estimated at approximately 8–10 weeks, whereas under community education scenarios, this delay is reduced to 3–5 weeks. This substantial reduction in diagnostic and treatment delays shortens the period of infectiousness, thereby decreasing cumulative exposure within households and the wider community and contributing to reduced transmission.

3.9.3. Reduction in MDR Emergence

Lower treatment interruptions lead to fewer transitions from DS to MDR (DS → MDR), meaning fewer cases enter the resistance evolution pathway: DS → MDR → pre-XDR → XDR.

3.10. Simulation Scenario: Health Literacy Intervention

When community engagement is integrated into the model, simulation outputs over a 10-year horizon indicate substantial epidemiological benefits. These include an estimated 40–60% reduction in active drug-sensitive (DS) TB transmission and a 20–35% reduction in drug-resistant (DR) TB transmission. In addition, the expansion of resistant strains is slowed, with projections showing delayed or potentially prevented dominance of DR-TB within the population. Consequently, the proportion of resistant TB cases among all active infections is expected to decline or stabilize, depending on the intensity and sustained implementation of the community-engaged intervention.

3.11. Mechanism of Community Engagement in the Model

Community-engaged tuberculosis (TB) education differs fundamentally from standard health messaging by embedding participatory and context-specific approaches into the design and delivery of interventions. It incorporates co-creation of local knowledge, the involvement of peer educators and community health workers, participatory research processes, and engagement with trusted community leadership. These mechanisms enhance cultural relevance, trust, and ownership of health interventions, thereby improving behavioral uptake and sustained practice. As a result, community-engaged approaches are more effective than conventional top-down health campaigns in promoting meaningful and lasting changes in health-seeking behavior and treatment adherence.

3.12. Integration with the Socio-Ecological Model

The intervention operates across multiple, interconnected levels of the health system. At the individual level, it improves symptom recognition and timely care-seeking. At the household level, it strengthens infection prevention practices, including ventilation and cough etiquette. At the community level, it reduces stigma and promotes supportive norms around testing and treatment. At the health system level, it enhances linkage to care and continuity of services. Collectively, these

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multi-level changes act synergistically to reduce transmission, shorten infectious periods, and improve overall tuberculosis control.

3.13. Policy Implications

A modeling extension of the DS–DR tuberculosis transmission framework suggests that integrating tuberculosis health literacy through community-engaged education and research could significantly reduce transmission. By improving early symptom recognition, reducing stigma, and strengthening treatment adherence, community education interventions influence key epidemiological parameters, including the transmission coefficient (β), treatment initiation rate (γ), and resistance amplification parameter (α). Scenario simulations indicate that even modest reductions in transmission rates combined with earlier treatment initiation could reduce the effective reproduction number for drug-sensitive TB below the epidemic threshold, while also slowing the expansion of drug-resistant strains. These findings support integrating community-engaged education into TB control strategies as a complementary intervention alongside diagnostics, treatment, and genomic surveillance.

3.14. Modeling the Impact of Community-Engaged TB Health Literacy on Transmission

Social and behavioral determinants, including delayed care-seeking, incomplete treatment adherence, stigma, and limited knowledge about transmission pathways, strongly influence tuberculosis transmission. Community-engaged education programs that improve TB health literacy can influence several key epidemiological parameters within transmission models. In the drug-sensitive–drug-resistant (DS–DR) transmission framework developed in this study, community-engaged TB health literacy interventions influence three major mechanisms: earlier diagnosis and treatment initiation, improved treatment adherence, and reduced transmission through behavioral awareness.

First, improved health literacy can reduce the effective transmission rate by increasing awareness of cough etiquette, ventilation, early symptom recognition, and household infection control practices. In modeling terms, this reduces the effective contact transmission coefficient for both drug-sensitive and drug-resistant strains. Second, community education improves recognition of symptoms and willingness to seek care, thereby increasing the treatment initiation rate and shortening the infectious period. Because the basic reproduction number (R_0) is inversely related to the rate of treatment initiation, earlier diagnosis can substantially reduce transmission potential. Third, an improved understanding of treatment duration and adherence reduces treatment interruptions, which, in turn, lowers the probability that drug-sensitive infections will develop into drug-resistant infections during treatment. In the DS–DR transmission model, a reduction in the resistance amplification parameter represents this. Together, these mechanisms reduce the effective reproduction number and slow the expansion of resistant strains within the population.

3.15. Impact of Community TB Education on Transmission Dynamics

The modeling framework was used to simulate the potential impact of integrating community-engaged TB education into tuberculosis control strategies. Three scenarios were explored: baseline transmission without community intervention, a moderate community education intervention, and a high-intensity community engagement program.

In the baseline scenario, limited TB health literacy results in delayed diagnosis and prolonged infectious periods, allowing transmission to continue within communities. Under a moderate community education intervention, increased awareness improves early care-seeking behavior and treatment adherence, resulting in a gradual decline in transmission. Under a high-intensity community engagement scenario, widespread community participation in TB education and research substantially reduces transmission and accelerates the decline of active infections.

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The simulation results demonstrate that community-engaged health literacy programs have the potential to significantly reduce tuberculosis transmission by reducing the effective transmission rate and shortening the duration of infectiousness. These findings support integrating community-engaged education into TB control strategies as a complementary approach alongside diagnostics, treatment, and genomic surveillance.

Simulated trajectories of tuberculosis transmission (Figure 7) under three scenarios: baseline transmission without community intervention, moderate community education, and high-intensity community engagement. Increasing community engagement leads to progressively larger reductions in transmission.

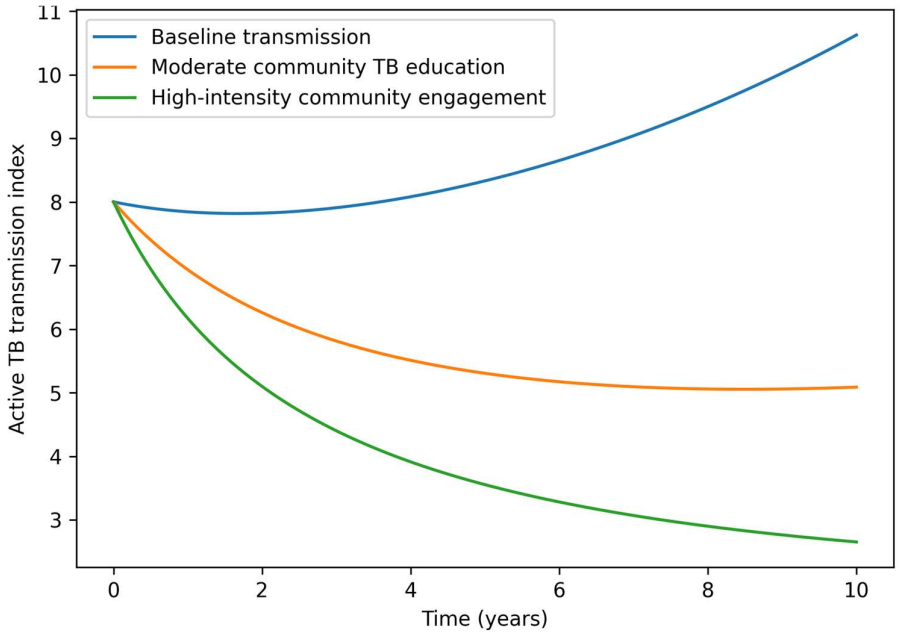

Figure 7. Impact of community-engaged tuberculosis education on transmission dynamics.

4. Discussion

This genomic analysis provides important insights into the transmission structure and resistance landscape of tuberculosis in the study population. The predominance of drug-resistant isolates, particularly MDR-TB, suggests that resistant TB transmission plays a substantial role in sustaining the local epidemic [31]. The dominance of Lineage 2 and Lineage 4 strains aligns with previous studies reporting the global epidemiological success of these lineages [32]. The Beijing lineage (Lineage 2) has frequently been associated with increased transmissibility, higher mutation rates, and a greater propensity to acquire drug resistance [33]. In the present dataset, lineage 2 isolates were disproportionately associated with pre-XDR and XDR resistance patterns, suggesting that this lineage may contribute significantly to the evolution of advanced drug resistance. These findings echoed those of similar studies conducted in other South African provinces, including the Eastern Cape [34,35]. The detection of canonical resistance mutations, including rpoB Ser450Leu, katG Ser315Thr, fabG1 −15C>T, gyrA Asp94 substitutions, and rrs 1401A>G, is consistent with previously documented global resistance mechanisms. The repeated occurrence of identical mutation combinations across multiple isolates provides indirect evidence that transmission of already resistant strains is occurring, rather than resistance emerging solely through treatment failure in individual patients, consistent with genomic epidemiological studies demonstrating that much of MDR and XDR-TB burden results from primary transmission of resistant *M. tuberculosis* strains [36,37].

These findings highlight the importance of integrating genomic surveillance with epidemiological modeling to understand better the dynamics of resistant TB transmission [34].

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Mathematical models that distinguish between drug-sensitive and drug-resistant transmission pathways can help quantify the relative contributions of primary transmission versus resistance amplification during treatment. Similar observations have been documented by Leibenberg et al. (2022), who emphasized the need for a coordinated approach in TB programs [31]. Such modelling frameworks are particularly valuable in high-burden settings where MDR-TB and XDR-TB threaten progress toward the WHO End TB Strategy. By incorporating genomic information into transmission models, it becomes possible to simulate how resistant strains spread through communities and evaluate the potential impact of interventions such as improved diagnostics, treatment adherence programs, and infection control strategies. Comparably, a scoping review on integrating genomic and spatial analyses to describe tuberculosis transmission discovered that integrating spatial and genomic data can provide a detailed understanding of local M tuberculosis transmission patterns; however, improved study designs and new analytical methods to address gaps in sampling completeness and integrate additional movement data are required to fully realize the potential of these tools [38,39]. However, this study has several limitations. The dataset provides a cross-sectional genomic snapshot, limiting the ability to infer transmission events definitively. Detailed epidemiological data, including sampling dates, geographic location, patient treatment history, and pairwise genomic distances, would be required to confirm recent transmission clusters and estimate transmission rates. In correspondence, a systematic analysis of transmission dynamics across global settings emphasized the quantification of individual-level heterogeneity and the further informed targeted intervention strategies [40]. Despite these limitations, the present findings strongly suggest that ongoing circulation of resistant strain families contributes significantly to the local TB burden, underscoring the need for strengthened surveillance and targeted public health interventions. Similarly, a study on global investment in TB genomic surveillance emphasizes the need to accelerate TB control by high-resolution mapping of transmission networks for targeted interventions. Further, it highlights the need to integrate machine learning with genomic and clinical data to tailor patient-specific management strategies [41].

4.1. Role of Community-Based Participatory Research (CBPR) in Tuberculosis Transmission Dynamics

4.1.1. Conceptual Integration: From Health Literacy to Participatory Systems Change

While this study demonstrates the value of integrating genomic surveillance and mathematical modeling to understand drug-resistant tuberculosis (DR-TB) transmission, the findings further highlight that transmission is not solely a biological phenomenon but is deeply embedded in social, structural, and behavioral systems.

Community-Based Participatory Research (CBPR) provides a critical framework for addressing these determinants by repositioning communities from passive recipients of interventions to active co-producers of knowledge and solutions. Unlike traditional top-down public health approaches, CBPR enables contextually grounded, socially responsive interventions that directly influence key epidemiological drivers of TB transmission. Recent evidence suggests that CBPR-informed interventions might increase trust between communities and health institutions, enhance case detection and treatment adherence, and enable more context-specific and equitable health initiatives. Furthermore, CBPR has been found to help identify contextually relevant solutions to complex public health challenges by integrating community priorities with scientific knowledge, resulting in more successful and sustainable disease control initiatives. CBPR techniques can help improve the implementation of infection prevention and control measures and assist targeted interventions in high-burden settings, such as those afflicted by drug-resistant tuberculosis [42,43]. This aligns with emerging evidence that TB screening and diagnostic innovations alone are insufficient when they fail to reach high-risk populations due to mistrust, stigma, and structural barriers.

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4.2. CBPR as a Mechanism for Modifying Transmission Parameters

Within the DS–DR transmission model developed in this study, CBPR does not operate as a peripheral intervention but as a systems-level modifier of epidemiological parameters. Correspondingly, adopting participatory systems modeling as a tool for implementation mapping in chronic illness prevention has been widely suggested [44–46].

4.2.1. Transmission Rate (β): Socially Mediated Reduction

CBPR-driven interventions enhance community understanding of TB transmission, promote the adoption of infection prevention behaviors such as improved ventilation and cough etiquette, and reduce stigma and social avoidance associated with the disease. Through co-created, contextually relevant messaging and community ownership, these interventions increase behavioral uptake and sustainability. Within the transmission model, this results in a reduction of the effective transmission coefficient (β), reflecting decreased contact-based transmission and contributing to overall epidemic control. Through co-created messaging and culturally embedded practices, CBPR reduces the effective transmission coefficient (β_s and β_r). Unlike conventional education, CBPR ensures behavioral uptake because interventions are locally owned and contextually meaningful. Similar findings were reported in a study in Cape Town, where participants at the community level advocated that TB survivors lead awareness-raising events and that TB material be included in the school curriculum. Policy measures aimed to reduce the visibility and stigma associated with a tuberculosis diagnosis in health facilities, as well as shift tasks to community health workers [47].

4.2.2. Treatment Initiation Rate (γ): Trust-Driven Acceleration

Delayed care-seeking is a major driver of TB transmission. CBPR addresses this challenge through trust-building between communities and health systems, community-led identification of barriers such as gender norms and work schedules, and the co-design of context-specific access strategies, including mobile clinics and after-hours testing. These interventions promote earlier diagnosis and more rapid treatment initiation, thereby shortening the infectious period and reducing the effective reproduction number, ultimately contributing to decreased transmission at the population level.

4.2.3. Resistance Amplification (α): Behavioral Control of Evolution

CBPR strengthens treatment adherence, improves patient understanding of treatment duration, and promotes peer-supported adherence systems within communities. By reducing treatment interruption and enhancing continuity of care, CBPR lowers the probability that drug-sensitive tuberculosis progresses to MDR and XDR forms during treatment. Within the transmission model, this effect is captured by reducing the resistance amplification parameter (α), thereby directly linking community-driven behavioral interventions to the evolutionary dynamics of drug resistance.

4.3. CBPR Process Model Applied to TB Transmission

CBPR operates through a **cyclical, iterative process** that aligns with dynamic transmission systems rather than static interventions.

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Table 1. Phase Integration into TB Control.

CBPR Phase	Transmission Relevance
Partnership & Trust Building	Improves healthcare engagement → reduces diagnostic delay
Co-identification of Problems	Identifies real drivers of transmission (e.g., under-testing of men)
Co-design of Interventions	Ensures context-specific strategies → increases uptake
Collaborative Data Collection	Enhances reach and surveillance quality
Co-analysis	Integrates lived experience into epidemiological interpretation.
Action & Intervention	Implements targeted transmission-reduction strategies
Dissemination	Improves community awareness and sustained behavior change
Reflection & Sustainability	Ensures long-term transmission control

This iterative structure reflects the nonlinear nature of TB transmission, in which behavioral and structural feedback loops continuously shape epidemic trajectories.

4.4. Methodological Implications: CBPR as Research Orientation

CBPR is not a discrete method but a research paradigm that shapes and informs methodological choices. In this study, CBPR complements genomic and transmission modeling approaches through the integration of qualitative methods, such as interviews and focus groups, to identify behavioral drivers of transmission; participatory tools, including community mapping and storytelling, to capture lived experiences; and co-designed quantitative surveys to generate policy-relevant data. These approaches are further strengthened through mixed-methods triangulation, enabling the integration of biological, social, and health system-level insights. This methodological pluralism enhances internal validity by ensuring contextual accuracy and strengthens external relevance by improving the applicability of findings to real-world policy and practice.

4.5. CBPR Within a Transdisciplinary TB Control Framework

The findings support a paradigm shift from multidisciplinary approaches, in which disciplines operate in parallel, and interdisciplinary models, which integrate academic knowledge, toward a fully transdisciplinary model that co-integrates biomedical science (including whole-genome sequencing and nucleic acid amplification tests), epidemiological modeling, social science, and community knowledge. In this framework, communities are not passive recipients but active participants, functioning as knowledge holders, co-researchers, and decision-makers. This transition is essential for addressing TB as a biosocial disease, enabling more contextually grounded, equitable, and effective interventions that respond to both biological and social drivers of transmission.

4.6. Impact Pathway: Linking CBPR to Transmission Reduction

CBPR influences TB transmission through a structured causal pathway:

Community engagement → Trust → Increased screening uptake → Early detection → Reduced infectious period → Reduced transmission → Slower resistance evolution. This pathway directly complements the DS–DR model by modifying upstream determinants that are otherwise unaddressed in purely biomedical frameworks.

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4.7. Integration with Genomic Surveillance and Modeling

The integration of CBPR into this study enhances the interpretation of genomic surveillance and transmission modeling findings by providing critical social and contextual insights. While genomic data reveals mutation clusters indicative of ongoing transmission of resistant strains, CBPR helps explain the underlying drivers of this persistence, including delayed diagnosis, limited healthcare access, and social barriers. In parallel, mathematical modeling demonstrates how targeted interventions can alter epidemic trajectories over time. Collectively, this integrated approach positions CBPR as a bridging framework that connects genomic evidence (what is happening biologically), transmission modeling (what could happen epidemiologically), and lived community realities (why it is happening socially), thereby enabling a more comprehensive and actionable understanding of tuberculosis dynamics.

4.8. Policy and Public Health Implications

The findings suggest that CBPR should be embedded as a core TB control strategy rather than treated as an adjunct activity. In high-burden rural settings, CBPR has the potential to improve the targeting of underserved populations, including men and remote communities, enhance the effectiveness and uptake of diagnostic tools such as nucleic acid amplification tests (NAATs), reduce treatment interruption and subsequent resistance emergence, and strengthen overall health system responsiveness and accountability. Importantly, CBPR reorients TB control efforts from a narrow focus on scaling diagnostic technologies toward achieving equitable, community-centered impact that addresses both biomedical and social drivers of the epidemic.

5. Study Limitations

The limited sample size may limit the analysis's statistical power and reduce the applicability of the results to larger populations, especially in heterogeneous, high-burden environments. Additionally, the use of cross-sectional genomic data limits our capacity to infer temporal transmission dynamics. WGS enables high-resolution identification of genomic clustering and resistance-associated mutations; however, the lack of longitudinal sampling limits the ability to distinguish between recent transmission and reactivation, as well as to reconstruct transmission chains with certainty. As a result, the findings should be considered as indicators of transmission patterns rather than conclusive evidence of a direct epidemiological relationship. Future research that integrates larger, longitudinally collected datasets with precise epidemiological and contact-tracing data would strengthen inferences about transmission patterns and improve the robustness of conclusions.

6. Recommendations

This study contributes to the evolving body of knowledge on tuberculosis by demonstrating the value of integrating genomic epidemiology, mathematical transmission modeling, and CBPR within a unified biosocial framework. Future research should build on this approach by developing hybrid models that explicitly incorporate social and behavioral determinants as dynamic parameters within transmission systems. There is a need for larger, longitudinal datasets that combine whole-genome sequencing, detailed epidemiological data, and community-level insights to improve inference on transmission pathways and resistance evolution. Additionally, operationalizing CBPR within quantitative models warrants further methodological refinement, including the development of standardized metrics to measure community engagement and its impact on epidemiological parameters, such as transmission, treatment initiation, and adherence. Comparative studies across different high-burden settings are also recommended to assess the generalizability of CBPR-informed modeling approaches. Ultimately, advancing TB research requires a shift toward transdisciplinary frameworks that move beyond purely biomedical paradigms to incorporate community knowledge as a critical component of disease control and health system strengthening.

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7. Conclusions

This study shows that incorporating CBPR into genomic and epidemiological frameworks yields a more comprehensive understanding of tuberculosis transmission patterns. By influencing key epidemiological indicators such as transmission rates, treatment initiation, and resistance amplification, CBPR serves as an important system-level intervention that can reduce both drug-sensitive and drug-resistant tuberculosis transmission. To achieve long-term TB control, future TB initiatives must move beyond segregated biomedical approaches and toward transdisciplinary, community-engaged models that integrate scientific innovation with lived realities.

Author Contributions: **Ncomeka Sineke** conceptualized the study, conducted the literature review, performed data analysis and interpretation, developed the transmission model, integrated the Community-Based Participatory Research (CBPR) framework into the analytical approach, and drafted the original manuscript. **Lindiwe Modest Faye** contributed to the study's conceptual refinement, interpretation of findings, and critical revision of the manuscript for important intellectual content. **Ntandazo Dlatu** contributed to methodological development, epidemiological modelling, interpretation of results, and critical review of the manuscript. **Saturnin Ombinda-Lemboumba** contributed to bioinformatics input and the critical revision of the manuscript. **Teke Apalata** supervised the study, contributed to the study design, the laboratory and genomic components, and the interpretation of findings, and critically reviewed and approved the final manuscript. All authors read, reviewed, and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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Institutional Review Board Statement: This study was conducted in accordance with the Declaration of Helsinki. Approval granted by the Research Ethics and Biosafety Committee of the Faculty of Health Sciences of Walter Sisulu University (Ref. No.140/202502; date July 2025) and Eastern Cape Department of Health (Reference Number EC_202507_022; date 11 July 2025).

Informed Consent Statement: Informed consent was not obtained from participants because the study was retrospective in nature and exclusively used archived, anonymized *M. tuberculosis* clinical isolates and corresponding routine programmatic data. All samples were de-identified prior to any analysis, and no personally identifiable information was handled. The need for individual patient consent was therefore waived in line with ethical guidelines for research on residual specimens.

Data Availability Statement: The data from this study are available upon request from the corresponding author.

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Conflicts of Interest: The authors declare no conflict of interest.

Abbreviation

AF	Allele Frequency
AIDS	Acquired Immunodeficiency Syndrome
AMPure XP	Agencourt AMPure XP Magnetic Beads
BWA	Burrows–Wheeler Aligner
CAS	Central Asian Strain
CBPR	Community-Based Participatory Research
DR-TB	Drug-Resistant Tuberculosis
DS-TB	Drug-Sensitive Tuberculosis
DNA	Deoxyribonucleic Acid
DOTS	Directly Observed Treatment, Short-course

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GATK	Genome Analysis Toolkit
HIV	Human Immunodeficiency Virus
H37Rv	*Mycobacterium tuberculosis* Reference Strain
LTBI	Latent Tuberculosis Infection
MDR-TB	Multidrug-Resistant Tuberculosis
Mtb	*Mycobacterium tuberculosis*
PCR	Polymerase Chain Reaction
pre-XDR-TB	Pre-Extensively Drug-Resistant Tuberculosis
RR-TB	Rifampicin-Resistant Tuberculosis
SNP	Single-Nucleotide Polymorphism
TB	Tuberculosis
TDR-TB	Totally Drug-Resistant Tuberculosis
USAP	Unified Sequence Analysis Pipeline
WHO	World Health Organization
WGS	Whole-Genome Sequencing
XDR-TB	Extensively Drug-Resistant Tuberculosis

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