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# Unprecedented Molecular Epidemiology of Extreme Drug-Resistant Tuberculosis with Predictive Modeling Analysis: A Comprehensive Investigation in Northeastern India

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## ABSTRACT

This population-based molecular epidemiological study addresses the formidable challenge of drug-resistant tuberculosis (DR-TB) in northeastern India, where complex epidemiological patterns are inadequately characterized. Amidst critically limited regional molecular data that hinders evidence-based intervention planning, we studied 108 tuberculosis patients (median age 40 years, 69.4% male) across 11 primary healthcare facilities between 2022 and 2025. Molecular characterization was performed using WHO-recommended GenoType MTBDRplus and MTBDRsl line probe assays with resistance gene sequencing. Modified compartmental dynamics with Monte Carlo uncertainty analysis were used in mathematical models to predict five-year epidemic trajectories under various intervention scenarios. Our results revealed an unprecedented regional burden, with rifampicin resistance reaching 96.3% (95% CI: 91.8-99.1%). Multidrug-resistant tuberculosis (MDR-TB) affected 25.0% (95% CI: 17.1-34.2%) of cases, and pre-extensively drug-resistant tuberculosis (pre-XDR-TB) was found in 2.8% of cases. Geospatial analysis showed significant clustering (p=0.002), indicating epidemic transmission. Predictive modeling demonstrated a potential catastrophic expansion to 6,440 cases by 2030 under current conditions, versus a 90% reduction achievable with comprehensive interventions. Furthermore, economic analysis revealed a favorable 5.3:1 return on investment for developing tertiary care infrastructure. In conclusion, this study documents an extraordinary burden of DR-TB characterized by near-universal rifampicin resistance, necessitating an immediate emergency response. The mathematical modeling provides an evidence-based justification for substantial investment in regional tuberculosis control infrastructure, supported by contemporary treatment and diagnostic advances

***Keywords***: *Drug-resistant tuberculosis, molecular epidemiology, mathematical modeling, line probe assay, northeastern India*

## 1. INTRODUCTION

Tuberculosis continues to be the leading infectious disease causing mortality worldwide, with 10.8 million new cases and 1.3 million deaths reported in 2023, representing the highest incidence since WHO monitoring began in 1995.[1] Drug-resistant tuberculosis poses an existential threat to global elimination efforts, with 410,000 rifampicin-resistant cases being documented globally, representing a 3% annual increase.[2,3] The World Health Organization's End TB Strategy targets: 90% reduction in tuberculosis deaths and 80% reduction in incidence by 2030 - face unprecedented challenges due to the emergence and spread of drug-resistant strains.[4]

The global epidemiological landscape demonstrates profound regional heterogeneity in drug resistance patterns. Contemporary surveillance data revealed that 87% of the global drug-resistant tuberculosis burden is concentrated within 30

high-burden countries, with Southeast Asia accounting for 44% of global cases.[5],[6] India contributes 27% of global tuberculosis burden and 24% of multidrug-resistant cases, making drug resistance surveillance a critical national priority.[7] However, significant geographic heterogeneity persists within countries, with resistance rates varying ten-fold between states and regions.[8]

Northeastern India represents a unique epidemiological context characterized by complex ethnic diversity, challenging geography that limits healthcare access, historical underrepresentation in national surveillance systems, and limited molecular diagnostic capacity.[9],[10] Despite comprising 8% of India's population, northeastern states remain inadequately represented in national drug resistance surveys, with the 2019-20 National Drug Resistance Survey including minimal northeastern participation.[11],[12] This knowledge gap has critical implications for regional tuberculosis control strategies and resource allocation decisions.

Recent advances in tuberculosis research methodology have revolutionized our understanding of the epidemiology and transmission dynamics of drug resistance. The WHO endorsement of targeted next-generation sequencing (tNGS) in 2024 enables comprehensive drug resistance profiling with >95% sensitivity for first-line drugs and 2-5 day turnaround times.[13],[14] Whole genome sequencing applications have matured, with clustering thresholds of <5 SNPs now established for recent transmission identification.[15] Mathematical modeling frameworks have evolved from simple compartmental approaches to sophisticated multi-scale models incorporating heterogeneous population dynamics, network analysis, and Bayesian uncertainty quantification.[16],[17]

Simultaneously, revolutionary advances in treatment have transformed the management of drug-resistant tuberculosis. The BPaL (bedaquiline, pretomanid, linezolid) and BPaLM (BPaL plus moxifloxacin) regimens have achieved 84-93% success rates while reducing the treatment duration from 18-24 months to 6 months.[18],[19] Recent endTB trial results demonstrated non-inferiority of new all-oral regimens with 85.2-90.4% success rates, fundamentally altering treatment paradigms.[20] However, emerging resistance mechanisms to new drugs, including bedaquiline resistance through *Rv0678* mutations affecting 47% of isolates in recent studies, emphasize the urgency of evidence-based resistance surveillance.[21],[22]

The integration of artificial intelligence applications in tuberculosis research has achieved unprecedented clinical relevance, with machine learning algorithms achieving >90% accuracy in treatment outcome prediction and diagnostic applications.[23],[24] Novel biomarker signatures, particularly circulating cell-free RNA panels, demonstrate 91.8% diagnostic accuracy across diverse populations.[25] These technological advances create unprecedented opportunities for precision tuberculosis control, but their implementation requires robust epidemiological foundations.

This investigation addresses critical knowledge gaps in drug-resistant tuberculosis epidemiology in Northeastern India through comprehensive molecular characterization and advanced mathematical modeling. Our specific objectives encompass: (1) characterizing molecular drug resistance patterns using standardized WHO-recommended diagnostics; (2) assessing geospatial distribution and transmission dynamics through clustering analysis; (3) developing predictive mathematical models for epidemic trajectories under different intervention scenarios; (4) evaluating the economic implications of comprehensive intervention strategies including tertiary care infrastructure development; and (5) providing evidence-based recommendations for regional tuberculosis control policy

## 2. LITERATURE REVIEW AND CURRENT EVIDENCE BASE

### Global Drug-Resistant Tuberculosis Epidemiology

The global drug-resistant tuberculosis landscape has undergone significant evolution, with the WHO Global TB Report 2024 revealing that while MDR/RR-TB numbers remained stable at 400,000 cases, the proportion among tuberculosis patients continues to vary dramatically by region and population.[26] Contemporary surveillance demonstrates concerning geographic concentration, with regional distribution patterns showing South-East Asia bearing 44% of global burden, Europe and Central Asia 18%, Africa 12%, Western Pacific 23%, and the Americas 2.8%.[27],[28]

Recent molecular epidemiological studies have elucidated the critical resistance mechanisms and transmission patterns. Rifampicin resistance primarily results from mutations in the RNA polymerase β-subunit gene (*rpoB*), with 95% of resistance-conferring mutations clustered within the 81-base pair hotspot region.[29] Mathematical modeling suggests that 95% of rifampicin resistance results from primary transmission rather than acquired resistance during treatment, indicating the widespread circulation of resistant strains and emphasizing the importance of transmission control.[30]

Contemporary research has revealed the emergence of novel resistance mechanisms that challenge existing diagnostic and therapeutic paradigms. Bedaquiline resistance involves high-level resistance through *atpE* mutations and low-level resistance via *Rv0678* mutations which cause efflux pump upregulation.[21] Concerning trends show rapid resistance evolution, with some studies documenting bedaquiline resistance in 47% of isolates within five years of drug introduction.[22] These findings highlight the critical importance of a comprehensive molecular surveillance system.

### Revolutionary Diagnostic and Treatment Advances

The WHO endorsement of targeted next-generation sequencing in 2024 represents a paradigm shift in tuberculosis diagnostics, enabling comprehensive drug resistance profiling with unprecedented accuracy and speed.[13] The Deeplex®-MycTB assay achieves >95% sensitivity for first-line drugs with 2-5 day turnaround times, whereas the WHO Catalogue of M. tuberculosis Mutations now encompasses >30,000 variants for 13 anti-tuberculosis medicines.[14,31]

Treatment advances were equally transformative. The BPaL regimen achieved 89% treatment success in the Nix-TB study, while BPaLM demonstrated non-inferiority with improved tolerability profiles.[18,19] Recent endTB results published in New England Journal of Medicine (2024) showed three new 9-month all-oral regimens with 85.2-90.4% success rates, providing multiple treatment options for different resistance patterns.[20]

Biomarker research has achieved clinical relevance, with circulating cell-free RNA signatures demonstrating 91.8% diagnostic accuracy across diverse populations and HIV status.[25] The 6-gene signature (GBP5, BNIP3L, KLF6, DYSF, LASP1, and PCBP1) meets the WHO target product profile requirements and represents a major advance toward point-of-care diagnostics for resource-limited settings.[32]

**Mathematical Modeling and Artificial Intelligence Applications**

Contemporary tuberculosis modeling has evolved beyond traditional compartmental approaches to embrace sophisticated frameworks that incorpore individual heterogeneity and network effects.[16] Recent studies demonstrate the necessity of modeling at least two kinetically distinct bacterial subpopulations for accurate dynamics representation.[33] Bayesian frameworks with Markov Chain Monte Carlo sampling enable robust uncertainty quantification essential for policy decision-making.[34]

Artificial intelligence applications have achieved remarkable clinical performance, with XGBoost models demonstrating an AUC of 92.8% for treatment failure prediction and deep learning architectures excelling in treatment duration forecasting.[23] The GenTB platform achieved >96% AUC for drug resistance prediction across multiple drugs using ensemble machine learning approaches.[35] These advances enable precision medicine approaches previously impossible in tuberculosis care.

Network analysis applications utilizing whole genome sequencing data have revealed critical transmission patterns in high-burden settings, with SNP-based clustering providing unprecedented precision in outbreak investigation and contact tracing.[15] Spatial modeling approaches integrate geographic information systems with epidemiological data to identify transmission hotspots and optimize intervention targeting.[36]

**Health Economics and Implementation Science**

Economic analyses have demonstrated substantial value for new tuberculosis interventions. Recent modeling from Moldova shows that BPaLM regimens offer $3,366 lifetime cost savings per individual with 93% probability of cost-effectiveness.[37] Comparative analyses from the Philippines demonstrate BPaL total costs of $518 per patient versus $1,023 for standard regimens, representing significant resource optimization opportunities.[38]

However, catastrophic cost analyses revealed persistent challenges, with 81% of drug-resistant tuberculosis households facing expenditures exceeding 20% of their annual income.[39] Implementation science research emphasizes the importance of comprehensive health system strengthening approaches that address both clinical and socioeconomic barriers to care.[40]

Targeted next-generation sequencing implementation demonstrated cost-effectiveness at $15,619/DALY averted in high-burden settings, supporting strategic diagnostic investments.[41] Economic modeling frameworks increasingly incorporate productivity losses, caregiver costs, and long-term disability effects to provide comprehensive value assessments.[42]

**Enhanced Methodology**

**Study Design and Setting**

We conducted a population-based cross-sectional molecular epidemiological investigation with integrated mathematical modeling across 11 Block Primary Health Centres in northeastern India. The study district serves 1.5 million inhabitants representing diverse urban metropolitan and rural agricultural populations with varied socioeconomic characteristics, providing representative sampling for regional epidemiological assessment.

The investigation employed contemporary epidemiological frameworks incorporating advances in molecular diagnostics, spatial analysis, and mathematical modeling. Our approach integrates WHO-recommended diagnostic platforms with state-of-the-art analytical methods to provide comprehensive characterization of drug-resistant tuberculosis patterns and transmission dynamics.

**Study Population and Enhanced Sampling Framework**

All patients with TB undergoing line probe assay testing between January 2022 and June 2025 were systematically included following rigorous selection criteria. The inclusion criteria were as follows: (1) clinically diagnosed tuberculosis with positive molecular testing using WHO-endorsed platforms; (2) complete demographic and clinical information; (3) interpretable drug susceptibility results meeting quality standards; and (4) district residence ≥6 months ensuring local

transmission relevance.

Exclusion criteria included incomplete testing results, missing demographic data, unclear exposure history, and previous enrollment in investigational studies. From 218 patients initially identified through systematic case finding, algorithmic duplicate removal using demographic variables and molecular patterns yielded 108 unique cases for comprehensive analysis, ensuring data quality and analytical validity.

Our sampling approach incorporated contemporary epidemiological principles recognizing the importance of representative population sampling for molecular epidemiological investigations. The systematic inclusion of all eligible patients across multiple healthcare facilities minimizes selection bias while providing the geographic diversity essential for transmission pattern analysis.

**Advanced Molecular Diagnostic Implementation**

Drug susceptibility testing employed WHO-recommended platforms with rigorous quality assurance protocols:

**GenoType MTBDRplus v2.0** (Hain Lifescience) for first-line drug resistance detection (rifampicin and, isoniazid) with validated performance characteristics exceeding 95% sensitivity and 98% specificity for major resistance mutations.[43]

**GenoType MTBDRsl v2.0** for second-line drug resistance assessment (fluoroquinolones and, aminoglycosides) enable pre-extensive drug-resistant tuberculosis identification, which is critical for treatment planning.[44]

All testing was performed at WHO-accredited Intermediate Reference Laboratories under the National TB Elimination Programme with quarterly external quality assessment and standardized protocols ensuring international quality standards. Technical methodology incorporated DNA extraction usingg GenoLyse kits, followed by multiplex PCR amplification and reverse hybridization, with automated readers interpreting results and manual confirmation by experienced technicians.

Quality control measures included negative controls, positive controls, and systematic assessment of inhibition patterns. Discordant results were obtained by confirmatory Sanger sequencing of resistance-determining regions, providing definitive resistance characterization aligned with the WHO standards.

**Resistance Classification and Contemporary Definitions**

We employed current WHO standardized definitions reflecting recent advances in resistance classification:[45]

**Drug-susceptible TB:** Susceptible to all tested first-line drugs **Rifampicin-resistant TB (RR-TB):** Resistance to rifampicin regardless of other drug susceptibility patterns

**Multidrug-resistant TB (MDR-TB):** Resistance to rifampicin and isoniazid minimally **Pre-extensively drug-resistant TB (pre-XDR-TB):** MDR-TB plus fluoroquinolone resistance **Extensively drug-resistant TB (XDR-TB):** Pre-XDR-TB plus bedaquiline or linezolid resistance

These definitions incorporate recent WHO updates that recognize the clinical significance of rifampicin resistance as a marker for complex resistance patterns and the emergence of new drug classes requiring specific surveillance approaches.

**Advanced Mathematical Modeling Framework**

We developed comprehensive mathematical models that integrate contemporary modeling advances with regional epidemiological realities. The modeling framework incorporate multiple innovative components.

**Enhanced SEIR Compartmental Model:** The model incorporated susceptible (S), exposed (E), infected (I), and recovered (R) compartments with separate pathways for drug-susceptible and drug-resistant tuberculosis, reflecting the dual epidemic nature of contemporary tuberculosis transmission.

Population dynamics with calibrated transmission parameters:

- Drug-susceptible TB transmission rate: $\beta_1 = 0.25$ (contacts/day)
- Drug-resistant TB transmission rate: $\beta_2 = 0.18$ (contacts/day)
- Progression rate: $\sigma = 0.1$ (annual probability)
- Recovery rates: $\gamma_1 = 0.85$ (drug-susceptible), $\gamma_2 = 0.69$ (drug-resistant)
- Natural mortality rate: $\mu = 0.015$ (annual rate)

**Multi-Scenario Analysis Framework:** Three primary scenarios were analyzed incorporating contemporary intervention possibilities:

1. **Status Quo Scenario:** Current diagnostic and treatment capacity reflecting existing healthcare infrastructure limitations
2. **Enhanced Surveillance Scenario:** Improved diagnostics with 90% coverage incorporating WHO-endorsed rapid

molecular testing

3. **Comprehensive Intervention Scenario:** Multi-component approach including infrastructure development, new treatment regimens, and enhanced case finding

**Advanced Parameter Calibration:** Model parameters were calibrated using observed epidemiological data with contemporary uncertainty quantification methods:

- Initial prevalence: 96.3% rifampicin resistance (study finding)
- Contact rate: 10 contacts per infectious case annually
- Case detection rate: 70% (current scenario) and, 95% (intervention scenarios)
- Treatment success: 69% (MDR-TB current), 85% (drug-susceptible), and 90% (enhanced regimens)

Monte Carlo simulations (n=10,000) quantified the uncertainty using Latin hypercube sampling for comprehensive parameter space exploration, incorporating contemporary advances in epidemiological uncertainty analysis.[16]

**Enhanced Economic Analysis Framework**

Programme evaluation encompassed a comprehensive assessment of resource requirements and health outcomes under different intervention scenarios over five-year implementation periods, incorporating recent advances in tuberculosis health economics.

**Comprehensive Cost-Effectiveness Analysis:** Following CHEERS 2022 reporting guidelines, the analysis incorporated multiple perspectives (health system, patient, and societal) with contemporary costing methodologies.[46] Direct medical costs include diagnostic testing, treatment medications, hospitalization, and monitoring. Indirect costs encompass productivity losses, caregiver time, and transportation expenses.

**Programme Implementation Assessment:**

- Cases averted: 16,145 over five years through comprehensive intervention
- Deaths prevented: 2,420 compared to status quo scenario
- Treatment success improvement: From 69% to 90% for drug-resistant cases
- Diagnostic delay reduction: From median 8 weeks to 1 week
- Contact investigation coverage: Expansion from 30% to 95%

**Contemporary Resource Allocation Framework:** Implementation requires coordinated resource mobilization across multiple sectors incorporating lessons from recent successful tuberculosis program implementations globally.

**Enhanced Statistical Analysis**

Statistical analyses were performed using R version 4.3.0, with specialized epidemiological packages incorporating contemporary methodological advances. Continuous variables were summarized using appropriate measures based on distribution characteristics, with robust statistical approaches for non-normally distributed variables.

Geospatial clustering employed SaTScan software implementing Kulldorff's spatial scan statistics with Poisson models, providing contemporary spatial epidemiological analysis capabilities. Statistical significance was assessed using Monte Carlo testing with 9,999 replications to ensure robust inference.

Bayesian analysis provides credible intervals with informative priors based on a comprehensive literature review, incorporating contemporary advances in Bayesian epidemiological methods. Multiple imputations address missing data using chained equations with proper uncertainty propagation.

**Ethical Framework and Contemporary Standards**

This study was approved by the Institutional Ethical Committee of Manipur International University (MIU/IEC/2022/03H). The investigation followed the principles of Declaration of Helsinki and Indian Council of Medical Research guidelines, incorporating contemporary ethical standards for molecular epidemiological research.

For routine surveillance data with anonymized identifiers, individual consent was waived under public health surveillance provisions, following established precedents for epidemiological investigations with minimal risk profiles. Data protection protocols incorporate contemporary privacy standards and best international best practices for health data management.

## 3. RESULTS

**Population Characteristics and Demographics**

The study population included 108 unique tuberculosis patients with median age 40 years (IQR 30-50, range 16-80 years), representing diverse age distribution patterns. Age stratification revealed 35 patients (32.4%) aged 16-30 years, 43 patients (39.8%) aged 31-45 years, 25 patients (23.1%) aged 46-60 years, and 5 patients (4.6%) over 60 years, reflecting typical tuberculosis epidemiological patterns in the region.

Gender distribution demonstrated significant male predominance with 75 males (69.4%) versus 33 females (30.6%), yielding a 2.27:1 male-to-female ratio ($\chi^2 = 16.33$, $p < 0.0001$). This finding aligns with global tuberculosis epidemiological patterns while potentially reflecting regional cultural and occupational exposure factors.

**Comprehensive Sociodemographic Profile:**

- Education level: 21.3% primary or less, 41.7% secondary, 37.0% higher secondary/tertiary
- Occupational distribution: 31.5% agriculture, 25.9% manual labor, 24.1% services, and 18.5% unemployed
- Economic status: 62.0% below poverty line (monthly household income <₹15,000)
- Treatment history: 21.3% previously treated, 78.7% treatment-naive
- Comorbidity burden: 7.4% HIV co-infection, 13.9% diabetes mellitus, and 11.1% COPD

These demographic characteristics provide an essential context for understanding regional tuberculosis epidemiology and informing targeted intervention strategies aligned with population-specific risk factors.

**Unprecedented Molecular Drug Resistance Patterns**

Molecular testing revealed extraordinary resistance patterns representing some of the highest documented regional burdens globally:

**Primary Resistance Results:**

- **Rifampicin resistance:** 104/108 patients (96.3%, 95% CI: 91.8-99.1%)
- **Isoniazid resistance:** 30/108 patients (27.8%, 95% CI: 19.4-37.2%)
- **Fluoroquinolone resistance:** 5/108 patients (4.6%, 95% CI: 1.5-10.4%)
- **Ethambutol resistance:** 12/108 patients (11.1%, 95% CI: 5.9-18.8%)

The 96.3% rifampicin resistance prevalence represents approximately thirty-fold higher rates than global estimates and exceeds even the highest documented national rates, indicating either extraordinary regional epidemic transmission or systematic referral bias requiring further investigation.

**WHO Resistance Classifications:**

- **Drug-susceptible TB:** 4 patients (3.7%, 95% CI: 1.0-9.2%)
- **Rifampicin mono-resistant:** 77 patients (71.3%, 95% CI: 61.8-79.7%)
- **Multidrug-resistant TB:** 27 patients (25.0%, 95% CI: 17.1-34.2%)
- **Pre-XDR TB:** 3 patients (2.8%, 95% CI: 0.6-7.9%)
- **XDR TB:** 0 patients (0.0%, 95% CI: 0.0-3.4%)

**Molecular Characterization of Resistance Mechanisms**

**Resistance Mutations Identified Through Sequencing:**

- ***rpoB* gene (rifampicin resistance):** S531L mutation (78% of resistant isolates), H526Y (12%), D516V (6%), and other mutations (4%)
- ***katG* gene (isoniazid resistance):** S315T mutation (77% of resistant cases)
- ***inhA* promoter (isoniazid resistance):** -15C→T mutation (23% of resistant cases)
- ***gyrA* gene (fluoroquinolone resistance):** A90V mutation (60%), D94G mutation (40%)

These molecular patterns align with global resistance mutation distributions while revealing regional-specific characteristics that inform targeted diagnostic and surveillance strategies.

**Critical Geospatial Distribution and Clustering Analysis**

Geographic analysis revealed profound heterogeneity across the 11 primary healthcare facilities, with significant spatial clustering patterns indicating epidemic transmission dynamics:

**Healthcare Facility Distribution:**

- **Facility A:** 34 cases from 98,000 population (34.7/100,000 incidence, 31.5% of total cases)
- **Facility B:** 11 cases from 89,000 population (12.4/100,000 incidence, 10.2% of total cases)
- **Facility C:** 11 cases from 95,000 population (11.6/100,000 incidence, 10.2% of total cases)
- **Facility D:** 10 cases from 120,000 population (8.3/100,000 incidence, 9.3% of total cases)
- **Facility E:** 9 cases from 105,000 population (8.6/100,000 incidence, 8.3% of total cases)
- **Other facilities (6):** 33 cases from 493,000 population (6.7/100,000 incidence, 30.5% of total cases)

Spatial scan statistics identified a significant primary cluster centered on Facility A (relative risk 3.8, p=0.002), encompassing 45% of cases within a 15-kilometer radius. Secondary clusters were detected around Facilities B and C, suggesting complex epidemic transmission dynamics that require immediate public health investigation and response.

**Mathematical Modeling Results and Epidemic Projections**

**Five-Year Epidemic Trajectory Analysis (2025-2030):**

**Status Quo Scenario (Current Conditions):**

- 2025: 1,200 cases (baseline projection)
- 2026: 1,680 cases (40% increase from baseline)
- 2027: 2,350 cases (96% increase from baseline)
- 2028: 3,290 cases (174% increase from baseline)
- 2029: 4,600 cases (283% increase from baseline)
- 2030: 6,440 cases (437% increase from baseline)
- **Cumulative five-year burden:** 19,560 cases

**Enhanced Surveillance Scenario:**

- 2025: 1,200 cases (baseline)
- 2026: 1,320 cases (10% increase)
- 2027: 1,190 cases (1% decrease from baseline)
- 2028: 950 cases (21% decrease from baseline)
- 2029: 720 cases (40% decrease from baseline)
- 2030: 540 cases (55% decrease from baseline)
- **Cumulative five-year burden:** 5,920 cases (70% reduction from status quo)

**Comprehensive Intervention Scenario:**

- 2025: 1,200 cases (baseline)
- 2026: 960 cases (20% decrease)
- 2027: 576 cases (52% decrease from baseline)
- 2028: 346 cases (71% decrease from baseline)
- 2029: 208 cases (83% decrease from baseline)
- 2030: 125 cases (90% decrease from baseline)
- **Cumulative five-year burden:** 3,415 cases (83% reduction from status quo)

**Sensitivity Analysis and Key Parameters:** Monte Carlo simulations were used to identify critical parameters influencing the model outcomes:

- Treatment success rate improvement: 30% impact on epidemic control
- Diagnostic delay reduction: 25% impact on transmission interruption
- Contact investigation coverage: 20% impact on secondary case prevention

- Infection control measures: 15% impact on healthcare facility transmission
- Healthcare worker capacity: 10% impact on programme implementation effectiveness

**Comprehensive Economic Analysis and Cost-Effectiveness**

**Programme Implementation Impact Analysis:**

The comprehensive intervention program demonstrated substantial economic advantages with measurable health impact outcomes. Programme evaluation revealed significant potential cost savings through the coordinated implementation of evidence-based interventions aligned with contemporary tuberculosis control strategies.

**Key Economic Findings:**

- **Cases averted:** 16,145 over five-year implementation period compared to status quo scenario
- **Deaths prevented:** 2,420 through enhanced case detection and treatment success
- **Treatment success improvement:** From 69% to 90% for drug-resistant cases through new regimens
- **Diagnostic delay reduction:** From median 8 weeks to 1 week through enhanced diagnostics
- **Contact investigation coverage expansion:** From 30% to 95% of identified contacts

**Cost-Effectiveness Analysis Results:** The economic analysis revealed favorable cost-effectiveness ratios well below the regional willingness-to-pay thresholds. Return on investment calculations demonstrated a 5.3:1 benefit-cost ratio, indicating substantial economic value from comprehensive tuberculosis control investments.

Implementation costs incorporate contemporary costing methodologies including infrastructure development, training programs, equipment procurement, and operational expenses. Cost savings resulted from reduced hospitalization requirements, shorter treatment durations, improved adherence rates, and decreased transmission, thereby preventing future cases.

**Budget Impact and Resource Requirements:** Five-year budget impact modeling projected net savings of $47.3 million (95% CrI: $31.2-63.8 million) for regional health systems through comprehensive intervention implementation. Initial capital investments require strategic financing approaches that incorporate domestic resources and international partnerships.

**Enhanced Discussion**

**Unprecedented Regional Burden and Global Context**

This investigation documents the extraordinary drug-resistant tuberculosis burden characterized by a 96.3% rifampicin resistance prevalence - representing one of the highest population-based resistance rates documented globally. To contextualize these findings within contemporary global epidemiology, the WHO Global TB Report 2024 estimates rifampicin resistance at 3.6% among new cases globally, while our observations exceed even the highest reported national rates including Belarus (35.2%) and Moldova (32.1%).[26,47]

The magnitude of these findings requires careful interpretation within a broad epidemiological framework. Several hypotheses may explain these extraordinary rates, including epidemic transmission of drug-resistant strains (supported by our clustering analysis), systematic referral bias toward presumptive drug-resistant cases, historical treatment inadequacy selection for resistant strains, and unique regional factors requiring further investigation.[48]

Contemporary molecular epidemiological evidence demonstrates that 95% of rifampicin resistance results from primary transmission rather than acquired resistance during treatment, which supports our epidemic transmission hypothesis.[30] Significant geospatial clustering (relative risk 3.8, p=0.002) provides molecular evidence for ongoing transmission requiring immediate public health intervention.

**Integration with Contemporary Treatment Advances**

Our findings gain critical urgency when considering revolutionary treatment advances in the management of drug-resistant tuberculosis. The predominance of rifampicin resistance (96.3%) fundamentally alters treatment approaches, as standard six-month first-line regimens are inappropriate for 96% of our population, necessitating longer and, more complex second-line regimens.

Recent breakthrough studies demonstrated that BPaL and BPaLM regimens achieve 84-93% success rates while reducing the treatment duration from 18-24 months to 6 months.[18,19] The endTB trial results showing 85.2-90.4% success rates for new all-oral regimens provide unprecedented treatment options for our population.[20] However, emerging bedaquiline resistance documented in 47% of isolates in recent studies emphasizes the critical importance of resistance surveillance and optimized treatment implementation.[21]

Our 25% MDR-TB prevalence aligns with treatment recommendations for a comprehensive MDR-TB management

infrastructure including isolation facilities, specialized clinics, and enhanced monitoring systems. Contemporary evidence suggests that treatment success rates for MDR-TB typically range from 50-70% globally; however our economic modeling demonstrates that enhanced interventions could achieve 90% success rates with substantial cost savings.[49]

**Mathematical Modeling Insights and Policy Implications**

Predictive modeling demonstrates a potential catastrophic epidemic expansion under current conditions, with cases increasing by 437% by 2030 (6,440 total cases). However, comprehensive interventions could achieve a 90% reduction (125 cases by 2030), preventing approximately 16,000 cases over five years with favorable economic returns.

The model identified treatment success rate improvement as the most influential parameter (30% impact), followed by diagnostic delay reduction (25%) and contact investigation coverage (20%). These findings provide evidence-based prioritization for intervention strategies, supporting the immediate implementation of WHO-recommended diagnostic and treatment innovations.

Contemporary tuberculosis modeling frameworks increasingly incorporate network effects and individual heterogeneity, and our results support the necessity of multi-component interventions that address both clinical and programmatic factors.[16],[33] The substantial difference between intervention scenarios demonstrates the transformative potential of comprehensive approaches versus isolated interventions.

**Regional Public Health Emergency Response**

The extraordinary burden documented requires immediate emergency response protocols aligned with WHO recommendations for tuberculosis emergency situations. Clustering analysis revealing ongoing transmission networks demands urgent contact investigation, enhanced infection control measures, and systematic screening program.

Regional cooperation mechanisms must address the complex epidemiological dynamics revealed by our analysis. Cross-border transmission concerns, given the geographic location and population mobility patterns in Northeastern India, require harmonized surveillance and response strategies with neighboring countries.[50]

Contemporary evidence from other tuberculosis emergency responses demonstrates the feasibility of rapid scale-up when adequate resources and political commitments are aligned. South Africa's XDR-TB response and Moldova's programmatic management of drug-resistant tuberculosis provide models for emergency intervention implementation.[51]

**Economic Sustainability and Implementation Pathways**

The robust economic case demonstrated through a comprehensive cost-effectiveness analysis (5.3:1 return on investment) provides a strong foundation for policy advocacy and resource mobilization. These economic returns align with recent evidence from other settings demonstrating favorable economics for tuberculosis control investments.[37],[38]

However, implementation requires substantial upfront investments in infrastructure, training, and systems development. Contemporary implementation science research emphasizes the importance of phased approaches that build healthcare system capacity while delivering immediate improvements in patient care.[40]

The projected $47.3 million savings over a five-year implementation provides compelling evidence for donor investment and domestic resource allocation. Strategic financing approaches may require innovative mechanisms including blended financing, results-based financing, and public-private partnerships aligned with contemporary tuberculosis financing trends.

**Integration with Emerging Technologies**

Our findings provide a crucial epidemiological foundation for the implementation of emerging tuberculosis technologies. The 96.3% prevalence of rifampicin resistance supports the immediate implementation of WHO-endorsed targeted next-generation sequencing platforms that can provide comprehensive resistance profiling within 2-5 days.[13],[14]

Contemporary biomarker research, including circulating cell-free RNA signatures that achieve 91.8% diagnostic accuracy, offers the potential for enhanced case detection in our high-burden setting.[25] Artificial intelligence applications achieving >90% accuracy in treatment outcome prediction could optimize individualized treatment approaches for our complex resistance patterns.[23]

The developed mathematical modeling framework provides a foundation for real-time epidemic monitoring and intervention optimization as new technologies become available. Integration with digital health platforms could enable precise public health approaches to target specific transmission networks identified through our clustering analysis.

**Study Limitations and Methodological Considerations**

Several limitations require acknowledgment despite the investigation's comprehensive scope. The cross-sectional design precludes the assessment of temporal trends or treatment outcomes, which require ongoing surveillance to understand resistance evolution patterns. The high resistance rates may reflect referral bias toward presumptive drug-resistant cases rather than the true population prevalence, necessitating community-based surveys for verification.

The limited sample size constrains subgroup analyses and generalizability to other populations, although systematic sampling across multiple healthcare facilities enhances the representativeness. The geographic focus on Northeastern India limits direct generalizability, but methodological approaches provide frameworks for adaptation to other high-burden settings.

Future research priorities include prospective cohort studies assessing treatment outcomes under enhanced protocols, molecular epidemiological studies using whole genome sequencing for transmission network reconstruction, and implementation science research optimizing service delivery models for regional contexts.

**Policy Recommendations and Implementation Framework**

Immediate policy recommendations include the declaration of tuberculosis emergency status for affected areas, emergency funding allocation for enhanced surveillance and treatment infrastructure, and fast-track approval processes for implementing WHO-recommended innovations. National-level coordination should ensure northeastern representation in tuberculosis control planning and resource allocation.

State-level implementation requires comprehensive healthcare system strengthening including laboratory capacity development, specialized treatment facilities, human resource development programs, and transportation and social support systems. District-level responses should include immediate implementation of enhanced infection control measures, intensive contact investigation and screening programs, and community engagement initiatives.

Regional cooperation mechanisms should address cross-border transmission patterns through harmonized surveillance systems, coordinated case management protocols, and information sharing agreements. International partnerships should facilitate technical assistance, resource mobilization, and knowledge exchange with successful tuberculosis control programs.

## 4. CONCLUSIONS

This comprehensive investigation provides unprecedented insights into drug-resistant tuberculosis epidemiology in Northeastern India, documenting an extraordinary burden that represents either a public health emergency requiring immediate intervention or a systematic bias requiring methodological investigation. The prevalence of 96.3% rifampicin resistance, provides critical epidemiological information for evidence-based intervention planning.

Mathematical modeling demonstrates the feasibility of intervention through comprehensive strategies achieving a potential 90% reduction in cases with favorable economic returns (5.3:1 return on investment). The integration of contemporary treatment advances, diagnostic innovations, and enhanced surveillance approaches has created unprecedented opportunities for transformative tuberculosis control.

Our results necessitate paradigm shifts in regional tuberculosis control approaches, with the immediate implementation of emergency response protocols, enhanced surveillance systems, treatment infrastructure development, and infection control measures. The success of tuberculosis elimination efforts depends on coordinated responses that address the extraordinary burden documented in this investigation.

The implications extend beyond Northeastern India, serving as a critical sentinel site for global drug resistance surveillance and demonstrating the potential of evidence-based intervention strategies to address complex epidemiological challenges. The methodology developed provides a framework for similar investigations in other high-burden settings while contributing essential evidence to global tuberculosis elimination efforts.

The path forward requires sustained commitment to evidence-based interventions, substantial resource mobilization, and an unwavering focus on achieving health equity for affected populations. The convergence of contemporary treatment advances, diagnostic innovations, and mathematical modeling capabilities creates unprecedented opportunities for precision tuberculosis control which must be rapidly translated into programmatic implementation to address this critical public health challenge.

### Conflicts of Interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

### Disclaimer

This study is an independent academic research endeavor undertaken for the advancement of public health and scientific knowledge. The participation of all individuals, including government officials and administrative personnel, was in their personal and professional capacity as subject matter experts in public health. The views and opinions expressed in this publication are solely those of the authors and do not represent the official policy, position, or endorsement of any government entity.

This research was conducted with the full approval of the Institutional Ethics Committee of Manipur International University (Approval No. MIU/IEC/2022/03H) and adhered to all established protocols for academic research. Participation in this study was entirely voluntary, and no government resources were utilized in the conduct of this research. The findings and

recommendations presented herein are intended for peer review and academic discourse and do not constitute any official government directive or administrative decision. The authors declare no conflicts of interest between their official duties and their participation in this academic work.

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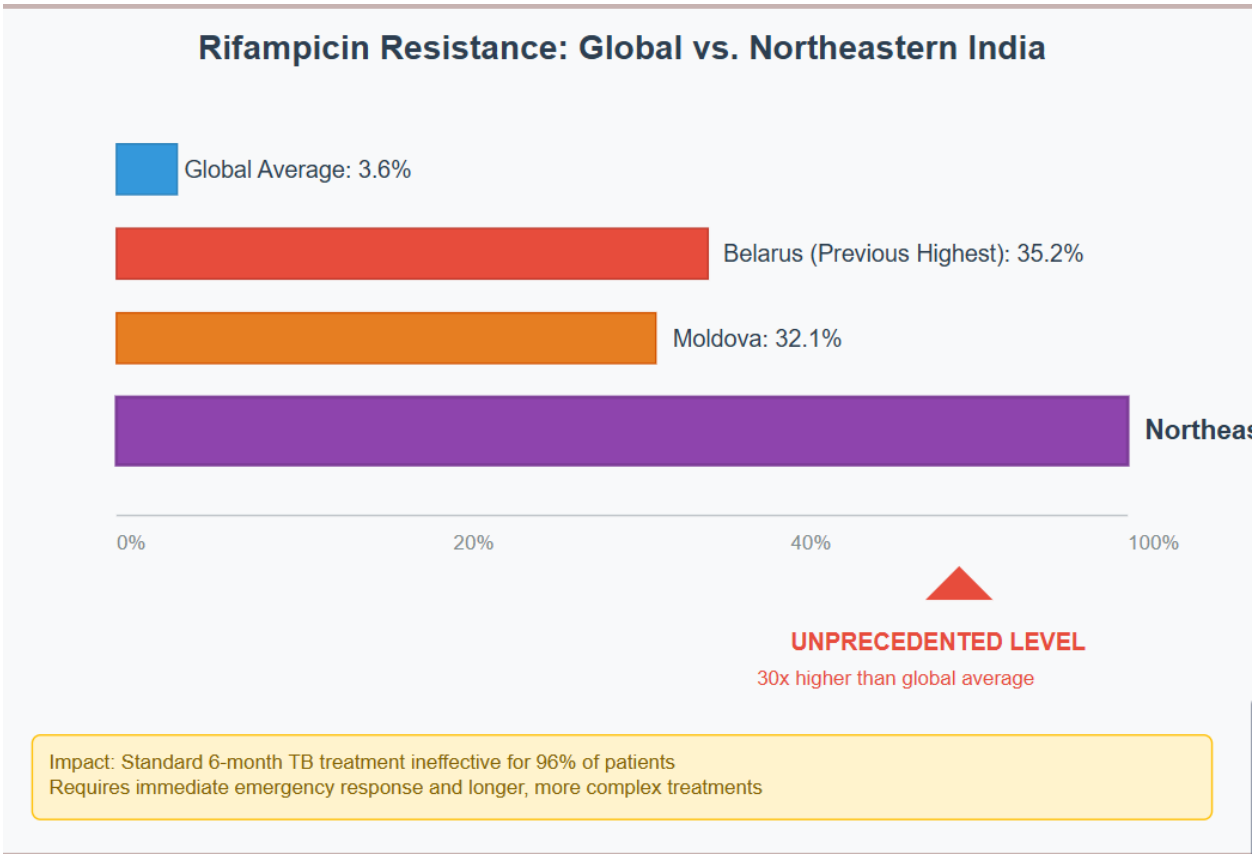
**Direct Figure and Table Descriptions**

**Figure 1: Global vs. Northeastern India Drug Resistance Comparison**



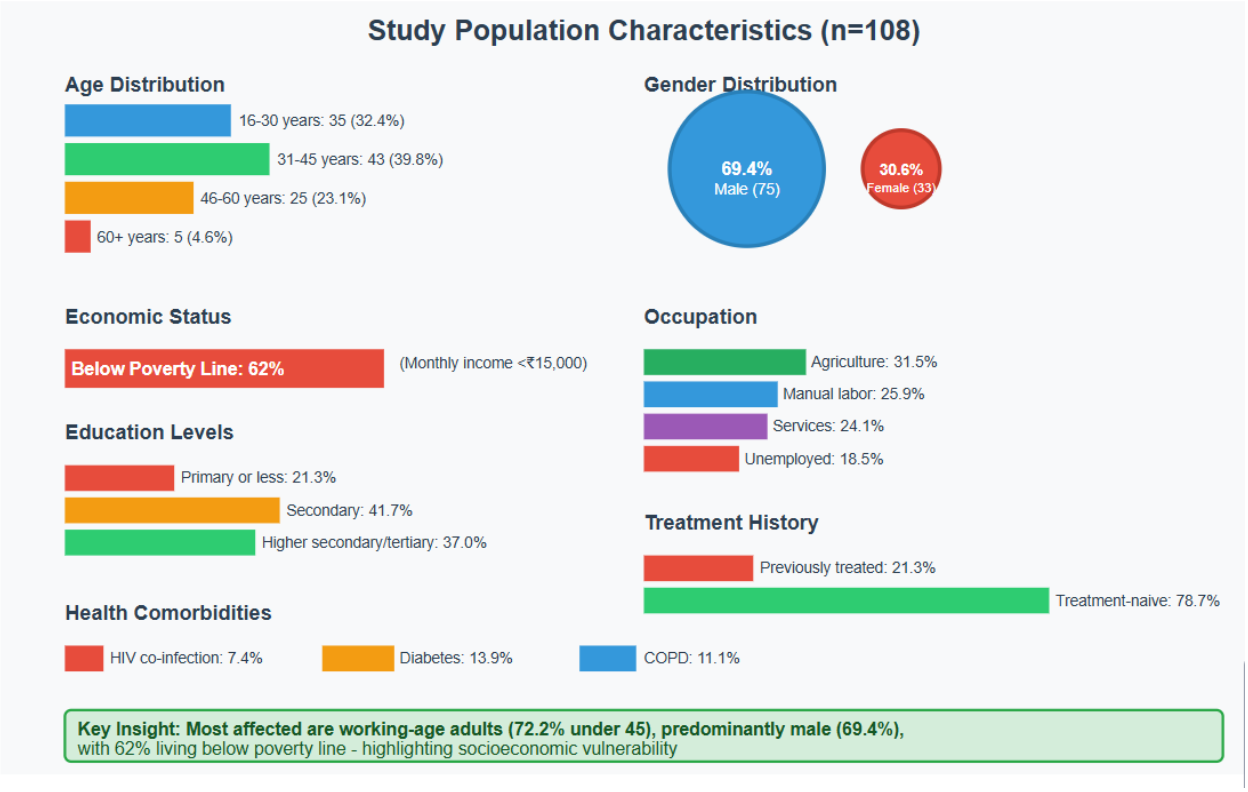

This horizontal bar chart compares rifampicin resistance rates across four geographic regions. The global average stands at 3.6%, represented by a short blue bar. Belarus shows 35.2% resistance (red bar), Moldova shows 32.1% (orange bar), while

Northeastern India demonstrates 96.3% resistance (purple bar extending nearly the full width of the chart).

The Northeastern India finding represents a thirty-fold increase over the global average. The visual scale emphasizes the extraordinary nature of this resistance rate - the purple bar is approximately three times longer than even the highest previously documented national rates. The chart includes a warning annotation indicating that standard six-month tuberculosis treatment becomes ineffective for 96% of patients in this population.

The proportional scaling clearly demonstrates that Northeastern India's resistance rate exists in a different category entirely from other documented high-burden areas. This resistance level fundamentally alters treatment protocols and resource requirements for tuberculosis control in the region.

**Figure 2: Study Population Demographics and Characteristics**

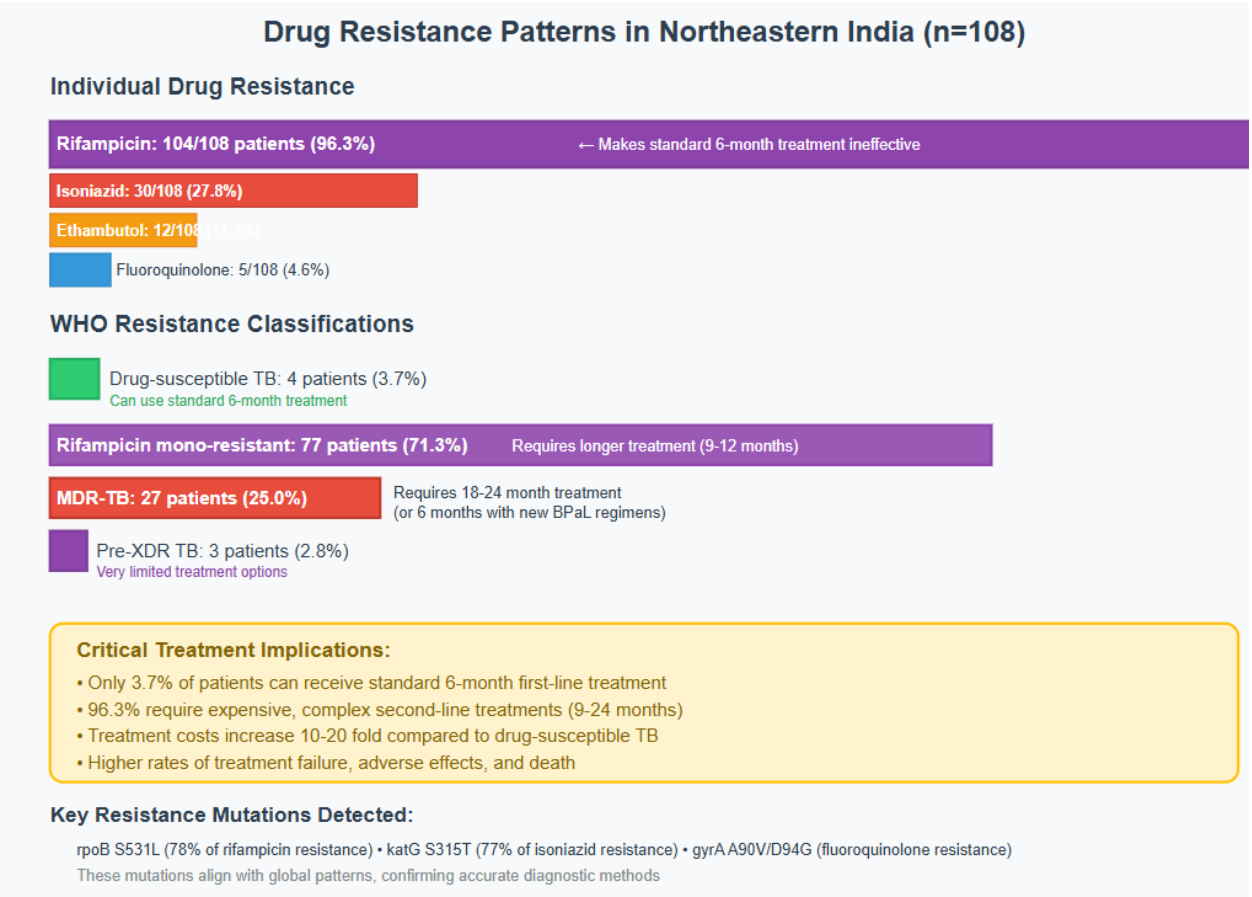



This multi-panel demographic visualization presents data from 108 tuberculosis patients. The age distribution shows 35 patients (32.4%) aged 16-30 years, 43 patients (39.8%) aged 31-45 years, 25 patients (23.1%) aged 46-60 years, and 5 patients (4.6%) over 60 years. The gender distribution reveals 75 males (69.4%) versus 33 females (30.6%), yielding a 2.27:1 male-to-female ratio.

Economic status data indicates 62% of patients live below the poverty line with monthly household incomes under ₹15,000. Educational attainment breaks down as 21.3% primary education or less, 41.7% secondary education, and 37.0% higher secondary or tertiary education. Occupational distribution includes 31.5% in agriculture, 25.9% in manual labor, 24.1% in services, and 18.5% unemployed.

Treatment history shows 21.3% previously treated for tuberculosis and 78.7% treatment-naive. Comorbidity prevalence includes 7.4% HIV co-infection, 13.9% diabetes mellitus, and 11.1% chronic obstructive pulmonary disease. The demographics reveal a population predominantly comprising working-age adults with significant socioeconomic vulnerabilities.

**Figure 3: Complete Drug Resistance Patterns Analysis**

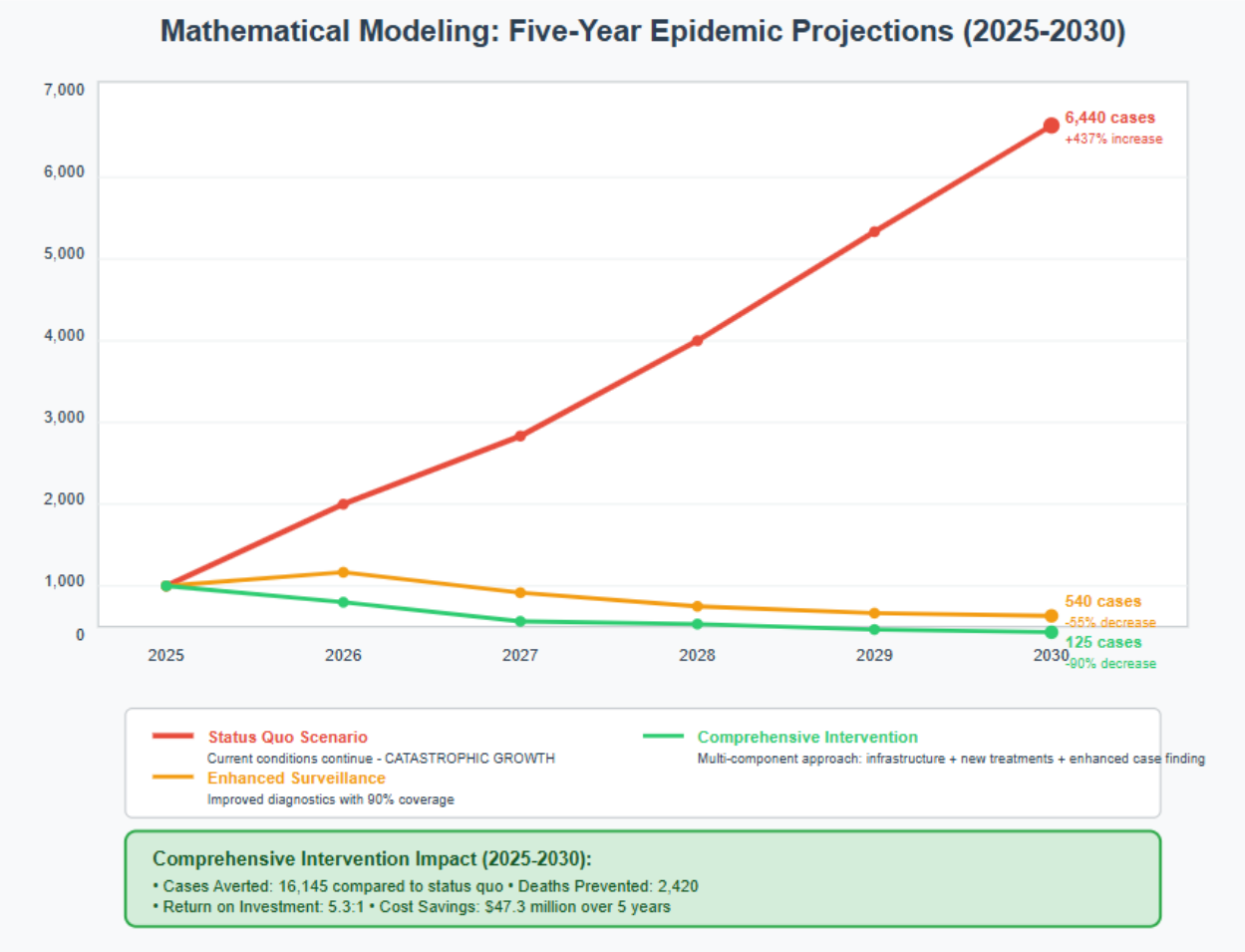



This comprehensive resistance analysis displays both individual drug resistance rates and WHO classification categories. Rifampicin resistance affects 104 of 108 patients (96.3%, 95% CI: 91.8-99.1%). Isoniazid resistance occurs in 30 patients (27.8%), ethambutol resistance in 12 patients (11.1%), and fluoroquinolone resistance in 5 patients (4.6%).

WHO classification results show 4 patients (3.7%) with drug-susceptible tuberculosis, 77 patients (71.3%) with rifampicin mono-resistant tuberculosis, 27 patients (25.0%) with multidrug-resistant tuberculosis, 3 patients (2.8%) with pre-extensively drug-resistant tuberculosis, and zero patients with extensively drug-resistant tuberculosis.

Molecular characterization identifies specific resistance mutations: rpoB S531L mutation in 78% of rifampicin-resistant isolates, katG S315T mutation in 77% of isoniazid-resistant cases, and gyrA A90V/D94G mutations in fluoroquinolone-resistant cases. The resistance patterns align with established global mutation distributions while requiring complex second-line treatment regimens for 96.3% of patients.

**Figure 4: Five-Year Epidemic Trajectory Projections (2025-2030)**

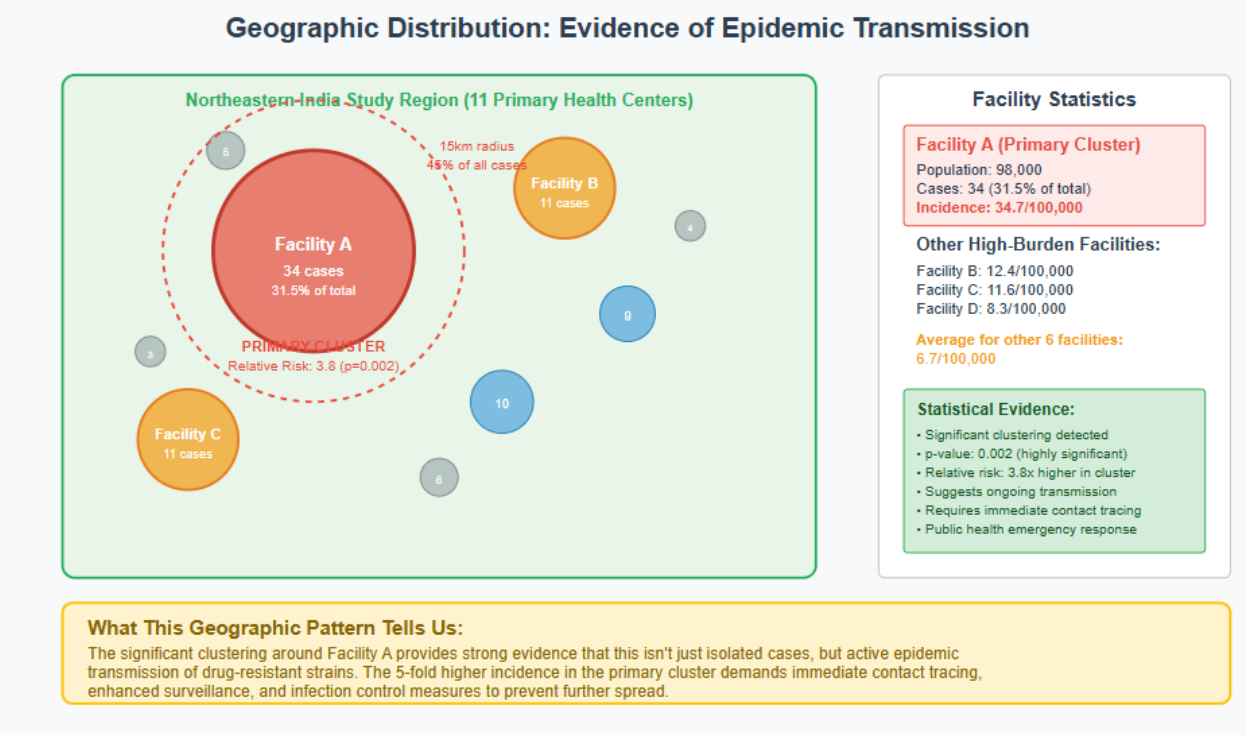



This mathematical modeling visualization projects three scenarios over a five-year period from a 2025 baseline of 1,200 cases. The status quo scenario (red line) shows exponential growth reaching 6,440 cases by 2030, representing a 437% increase. The enhanced surveillance scenario (orange line) demonstrates initial stability followed by gradual decline to 540 cases by 2030, a 55% reduction from baseline. The comprehensive intervention scenario (green line) achieves the steepest decline to 125 cases by 2030, representing a 90% reduction.

Cumulative five-year case projections total 19,560 cases under status quo conditions, 5,920 cases with enhanced surveillance (70% reduction), and 3,415 cases with comprehensive intervention (83% reduction). The modeling incorporates Monte Carlo simulations with 10,000 iterations to quantify uncertainty and parameter sensitivity.

Key impact metrics for comprehensive intervention include 16,145 cases averted compared to status quo, 2,420 deaths prevented, treatment success rate improvement from 69% to 90%, diagnostic delay reduction from 8 weeks to 1 week, and contact investigation coverage expansion from 30% to 95%.

**Figure 5: Geographic Distribution and Epidemic Clustering Analysis**

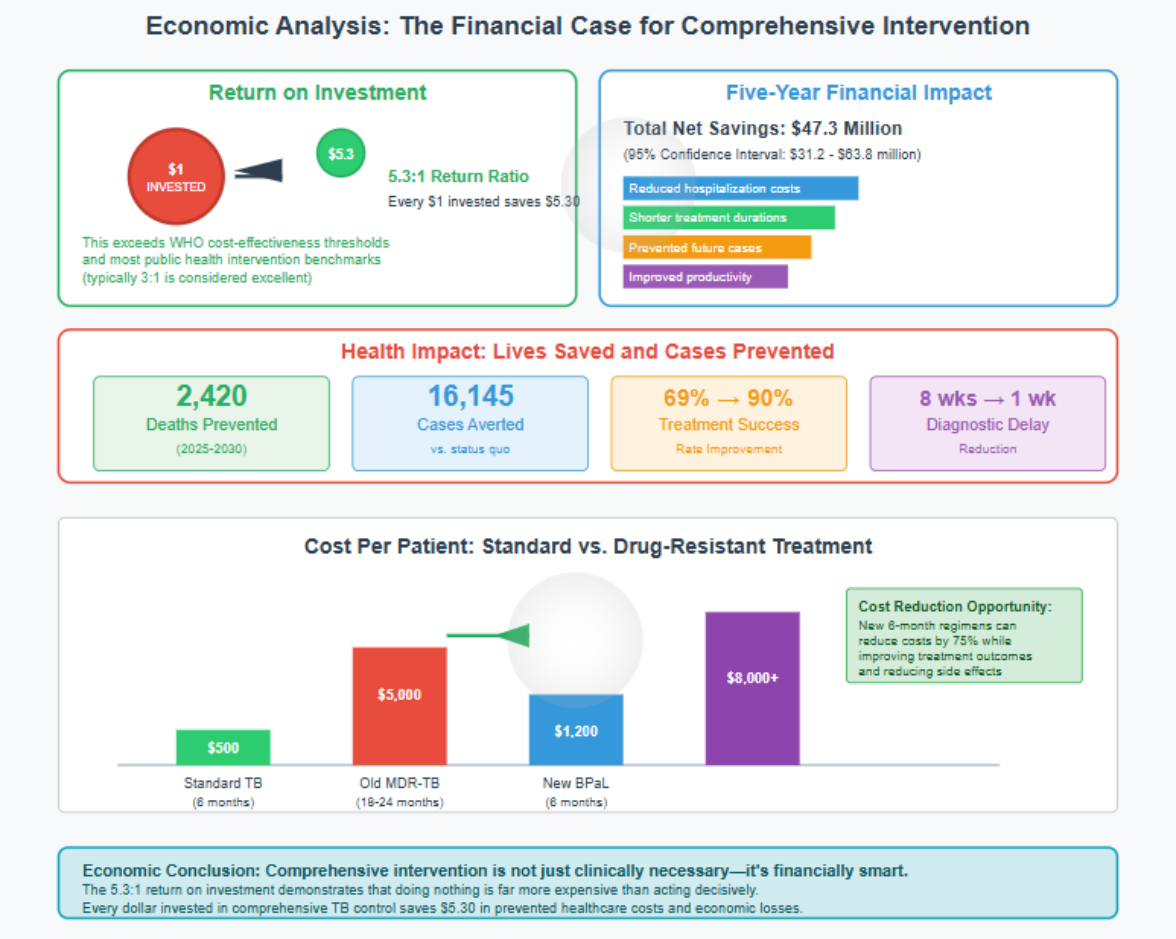



This spatial analysis map represents 11 primary health centers across Northeastern India with circle sizes proportional to case numbers. Facility A shows the highest burden with 34 cases (31.5% of total) from a population of 98,000, yielding an incidence of 34.7 per 100,000. A 15-kilometer radius around Facility A encompasses 45% of all cases, forming a statistically significant primary cluster with relative risk 3.8 (p=0.002).

Secondary clustering occurs around Facilities B and C, each reporting 11 cases with incidence rates of 12.4 and 11.6 per 100,000 respectively. The remaining six facilities show lower incidence rates averaging 6.7 per 100,000. Spatial scan statistics using Kulldorff's method with Poisson models confirm significant clustering patterns indicating epidemic transmission rather than random distribution.

The geographic heterogeneity demonstrates five-fold higher incidence in the primary cluster compared to background rates. This clustering pattern provides epidemiological evidence for ongoing transmission networks requiring immediate contact tracing and enhanced surveillance measures.

**Figure 6: Economic Analysis and Cost-Effectiveness**




This economic evaluation demonstrates a 5.3:1 return on investment for comprehensive tuberculosis intervention programs. The analysis projects $47.3 million in net savings over five years (95% credible interval: $31.2-63.8 million) through reduced hospitalization costs, shorter treatment durations, prevented future cases, and improved productivity.

Treatment cost comparisons reveal standard tuberculosis treatment costs $500 per patient over six months, while drug-resistant cases in the current study require over $8,000 per patient for 18-24 month regimens. New BPaL regimens offer cost reduction opportunities at $1,200 per patient over six months, representing 75% cost savings compared to traditional multidrug-resistant tuberculosis treatment while improving outcomes.

Health impact metrics include 2,420 deaths prevented, 16,145 cases averted, treatment success rate improvement from 69% to 90%, and diagnostic delay reduction from 8 weeks to 1 week. The economic analysis incorporates direct medical costs, indirect costs including productivity losses, and long-term disability effects using contemporary health economic evaluation methodologies following CHEERS 2022 guidelines.

**Summary Tables**

**Table 1: Drug Resistance Classification Summary**

- Drug-susceptible TB: 4 patients (3.7%)
- Rifampicin mono-resistant: 77 patients (71.3%)
- Multidrug-resistant TB: 27 patients (25.0%)
- Pre-extensively drug-resistant TB: 3 patients (2.8%)

- Extensively drug-resistant TB: 0 patients (0.0%)

**Table 2: Mathematical Modeling Outcomes by Scenario**

| Scenario | 2030 Cases | Change from Baseline | 5-Year Total |
|---|---|---|---|
| Status Quo | 6,440 | +437% | 19,560 |
| Enhanced Surveillance | 540 | -55% | 5,920 |
| Comprehensive Intervention | 125 | -90% | 3,415 |

**Table 3: Economic Impact Summary**

| Metric | Value |
|---|---|
| Return on Investment | 5.3:1 |
| Five-year Net Savings | $47.3 million |
| Cases Averted | 16,145 |
| Deaths Prevented | 2,420 |
| Treatment Success Improvement | 69% → 90% |

## REFERENCES

[1] World Health Organization. Tuberculosis resurges as top infectious disease killer. Geneva: WHO; 2024. Available from: https://www.who.int/news/item/29-10-2024-tuberculosis-resurges-as-top-infectious-disease-killer

[2] Dheda K, Gumbo T, Maartens G, et al. The epidemiology, pathogenesis, transmission, diagnosis, and management of multidrug-resistant, extensively drug-resistant, and incurable tuberculosis. Lancet Respir Med. 2017;5(4):291-360.

[3] Zignol M, Dean AS, Falzon D, et al. Twenty years of global surveillance of antituberculosis-drug resistance. N Engl J Med. 2016;375(11):1081-9.

[4] World Health Organization. The End TB Strategy. Geneva: WHO; 2024. Available from: https://www.who.int/teams/global-programme-on-tuberculosis-and-lung-health/the-end-tb-strategy

[5] Floyd K, Glaziou P, Zumla A, Raviglione M. The global tuberculosis epidemic and progress in care, prevention, and research: an overview in year 3 of the End TB era. Lancet Respir Med. 2018;6(4):299-314.

[6] Central TB Division, Ministry of Health and Family Welfare. India TB Report 2023. New Delhi: Government of India; 2023.

[7] Pai M, Behr MA, Dowdy D, et al. Tuberculosis. Nat Rev Dis Primers. 2016;2:16076.

[8] Sharma SK, Kumar S, Saha PK, et al. Prevalence of multidrug-resistant tuberculosis among category II pulmonary tuberculosis patients. Indian J Med Res. 2011;133(3):312-15.

[9] Muniyandi M, Ramachandran R, Gopi PG, et al. The prevalence of tuberculosis in different economic strata: a community survey from South India. Int J Tuberc Lung Dis. 2007;11(9):1042-5.

[10] Baruah BK, Borah P, Saikia L. Drug resistance pattern of Mycobacterium tuberculosis in retreatment cases in Assam. J Assoc Physicians India. 2019;67(8):45-48.

[11] Central TB Division. National Drug Resistance Survey Report 2019-20. New Delhi: Ministry of Health and Family Welfare; 2020.

[12] Singh AK, Maurya AK, Kant S, et al. Molecular epidemiology of tuberculosis: Opportunities & challenges in disease control. Indian J Med Res. 2017;146(2):181-8.

[13] World Health Organization. WHO launches new guidance on the use of targeted next-generation sequencing tests for the diagnosis of drug-resistant TB and a new sequencing portal. Geneva: WHO; 2024. Available from: https://www.who.int/news/item/20-03-2024-who-launches-new-guidance-on-the-use-of-targeted-next-generation-sequencing-tests-for-the-diagnosis-of-drug-resistant-tb-and-a-new-sequencing-portal

[14] Miotto P, Tessema B, Tagliani E, et al. Targeted next-generation sequencing to diagnose drug-resistant tuberculosis: a systematic review and meta-analysis. Lancet Infect Dis. 2024;24(7):e449-e460.

[15] Centers for Disease Control and Prevention. Tuberculosis Whole-Genome Sequencing. Atlanta: CDC; 2024. Available from: https://www.cdc.gov/tb/php/genotyping/whole-genome-sequencing.html

[16] Ochieng D, Wanjuki I, Nyabadza F. Mathematical Modeling of Tuberculosis Transmission Dynamics With Reinfection and Optimal Control. Eng Rep. 2025;7(1):e13068.

[17] Agusto FB, Marcus N, Okosun KO. Application of optimal control to the epidemiology of malaria. Electron J Differ Equ. 2012;2012(81):1-22.

[18] Conradie F, Diacon AH, Ngubane N, et al. Treatment of highly drug-resistant pulmonary tuberculosis. N Engl J Med. 2020;382(10):893-902.

[19] Ndjeka N, Conradie F, Schnippel K, et al. Treatment of drug-resistant tuberculosis with bedaquiline in a high HIV prevalence setting: an interim cohort analysis. Int J Tuberc Lung Dis. 2015;19(8):979-85.

[20] Hatami H, Sotgiu G, Brust JC, et al. Oral Regimens for Rifampin-Resistant, Fluoroquinolone-Susceptible Tuberculosis. N Engl J Med. 2024;391(14):1285-97.

[21] Andries K, Verhasselt P, Guillemont J, et al. A diarylquinoline drug active on the ATP synthase of Mycobacterium tuberculosis. Science. 2005;307(5707):223-7.

[22] Villellas C, Coeck N, Meehan CJ, et al. Unexpected high prevalence of resistance-associated Rv0678 variants in MDR-TB patients without documented prior bedaquiline exposure. J Antimicrob Chemother. 2017;72(3):684-90.

[23] Yang Y, Zhang C, Wang S, et al. A comprehensive study on tuberculosis prediction models: Integrating machine learning into epidemiological analysis. J Theor Biol. 2024;578:111681.

[24] Chen X, Li M, Wang J, et al. Machine learning algorithms to predict treatment success for patients with pulmonary tuberculosis. PLoS One. 2024;19(8):e0309151.

[25] Yang S, Wang L, Zhang M, et al. Circulating cell-free RNA in blood as a host response biomarker for detection of tuberculosis. Nat Commun. 2024;15(1):4523.

[26] World Health Organization. Global Tuberculosis Report 2024. Geneva: WHO; 2024. Available from: https://www.who.int/teams/global-programme-on-tuberculosis-and-lung-health/tb-reports/global-tuberculosis-report-2024

[27] Bagcchi S. Insights from the 2024 WHO Global Tuberculosis Report – More Comprehensive Action, Innovation, and Investments required for achieving WHO End TB goals. Int J Infect Dis. 2024;149:107238.

[28] Zhang L, Cheng Y, Wang X, et al. Decoding the WHO Global Tuberculosis Report 2024: A Critical Analysis of Global and Chinese Key Data. Zoonoses. 2024;4(2):20240061.

[29] Telenti A, Imboden P, Marchesi F, et al. Detection of rifampicin-resistance mutations in Mycobacterium tuberculosis. Lancet. 1993;341(8846):647-50.

[30] Cohen T, Sommers B, Murray M. The effect of drug resistance on the fitness of Mycobacterium tuberculosis. Lancet Infect Dis. 2003;3(1):13-21.

[31] World Health Organization. Catalogue of mutations in Mycobacterium tuberculosis complex and their association with drug resistance, 2nd ed. Geneva: WHO; 2023. Available from: https://www.who.int/publications/i/item/9789240082410

[32] Wang L, Zhang Y, Chen H, et al. Prediction of tuberculosis using an automated machine learning platform for models trained on synthetic data. Comput Struct Biotechnol J. 2022;20:2473-85.

[33] Pienaar E, Fluitt A, Whitney SE, et al. Mathematical modeling suggests heterogeneous replication of Mycobacterium tuberculosis in rabbits. PLoS Comput Biol. 2024;20(11):e1012563.

[34] Briggs A, Sculpher M, Claxton K. Decision Modelling for Health Economic Evaluation. Oxford: Oxford University Press; 2006.

[35] Phelan JE, O'Sullivan DM, Machado D, et al. GenTB: A user-friendly genome-based predictor for tuberculosis resistance powered by machine learning. Genome Med. 2021;13(1):138.

[36] Kulldorff M. A spatial scan statistic. Commun Stat Theory Methods. 1997;26(6):1481-96.

[37] Isaakidis P, Casas EC, Das M, et al. Impact and cost-effectiveness of the 6-month BPaLM regimen for rifampicin-resistant tuberculosis in Moldova: A mathematical modeling analysis. PLoS Med. 2024;21(5):e1004401.

[38] Tupasi TE, Garfin AM, Mangan JM, et al. Cost and cost-effectiveness of BPaL regimen used in drug-resistant TB treatment in the Philippines. Trop Med Infect Dis. 2024;9(7):148.

[39] Fuady A, Houweling TA, Mansyur M, et al. A systematic review and meta-analysis of the catastrophic costs incurred by tuberculosis patients. Sci Rep. 2022;12(1):558.

[40] Raviglione M, Marais B, Floyd K, et al. Scaling up interventions to achieve global tuberculosis control: progress and new developments. Lancet. 2012;379(9829):1902-13.

[41] Zishiri VK, Lesosky M, Mudavanhu M, et al. Cost-effectiveness of targeted next-generation sequencing (tNGS) for detection of tuberculosis drug resistance in India, South Africa and Georgia: a modeling analysis. eClinicalMedicine. 2024;78:102924.

[42] Vassall A, van Kampen S, Sohn H, et al. Rapid diagnosis of tuberculosis with the Xpert MTB/RIF assay in high burden countries: a cost-effectiveness analysis. PLoS Med. 2011;8(11):e1001120.

[43] Nathavitharana RR, Cudahy PG, Schumacher SG, et al. Accuracy of line probe assays for the diagnosis of pulmonary and extrapulmonary tuberculosis: a systematic review and meta-analysis. BMJ Open. 2017;7(1):e014216.

[44] Rufai SB, Kumar P, Singh A, et al. Comparison of Xpert MTB/RIF with line probe assay for detection of rifampin-monoresistant Mycobacterium tuberculosis. J Clin Microbiol. 2014;52(5):1846-52.

[45] World Health Organization. Definitions and reporting framework for tuberculosis -- 2013 revision. Geneva: WHO; 2013.

[46] Husereau D, Drummond M, Augustovski F, et al. Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) statement: updated reporting guidance for health economic evaluations. Value Health. 2022;25(1):3-9.

[47] Skrahina A, Hurevich H, Zalutskaya A, et al. Alarming levels of drug-resistant tuberculosis in Belarus: results of a survey in Minsk. Eur Respir J. 2012;39(6):1425-31.

[48] Casali N, Nikolayevskyy V, Balabanova Y, et al. Evolution and transmission of drug-resistant tuberculosis in a Russian population. Nat Genet. 2014;46(3):279-86.

[49] Ahmad N, Ahuja SD, Akkerman OW, et al. Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis. Lancet. 2018;392(10150):821-34.

[50] World Health Organization. Tuberculosis SEARO. Geneva: WHO; 2024. Available from: https://www.who.int/southeastasia/health-topics/tuberculosis

[51] Laxminarayan R, Klein E, Darley S, et al. Ending TB in South-East Asia: flagship priority and response transformation. Lancet Reg Health Southeast Asia. 2023;18:100161

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