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## 1.Evolution of Mycobacterium tuberculosis transcription regulation is associated with increased transmission and drug resistance.

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Update of
bioRxiv. 2025 May 01:2025.05.01.651750. doi: 10.1101/2025.05.01.651750.

Mycobacterium tuberculosis (Mtb) has co-evolved with humans for thousands of

years and is characterized by variation in virulence, transmissibility, and disease phenotypes. To identify bacterial contributors to phenotypic diversity, we developed new RNA sequencing (RNA-seq) and phylogenomic tools to capture hundreds of Mtb isolate transcriptomes, link transcriptional and genetic variation, and find associations between variants and epidemiologic traits. Across 274 Mtb clinical isolates, we uncovered unexpected diversity in virulence gene expression, which we linked to known and unknown regulators. Surprisingly, we found that many isolates harbor variants associated with decreased expression of EsxA (Esat6) and EsxB (Cfp10), which are virulence effectors, dominant T cell antigens, and immunodiagnostic targets. Across >55,000 isolates, these variants associate with increased transmissibility, especially in drug-resistant Mtb strains. Our data suggest expression of Mtb virulence genes is evolving in response to drug-linked pressure, raising concerns about use of these targets in immunodiagnostics and next-generation vaccines.



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**2. Molecular epidemiology of drug-resistant tuberculosis in Jiangxi Province, China, 2022-2023.**

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Drug-resistant tuberculosis (DR-TB) poses a critical public health challenge in

Jiangxi Province, China, where regional resistance patterns remain understudied. This retrospective study analyzed 9,041 suspected TB patients (2022-2023), identifying 3,104 Mycobacterium tuberculosis (M. tuberculosis) cases via PCR-reverse blot hybridization assay (PCR-REBA). Among M. tuberculosis-positive cases, 19.3% exhibited drug resistance, including mono- (9.2%), double- (4.6%), triple- (3.8%), and quadruple-drug resistance (1.7%). Males had higher odds of rifampicin (OR = 1.407, 95% CI: 1.086-1.824, p = 0.01) and isoniazid (OR = 1.959, 95% CI: 1.538-2.495, p < 0.001) resistance. Dominant mutations included rpoB Ser531Leu (32.1%) for rifampicin and katG Ser315Thr (53.6%) for isoniazid resistance. Extrapulmonary TB showed higher susceptibility than pulmonary TB (e.g., rifampicin: 93.47% vs. 87.25%, p = 0.002). These findings highlight the urgent need for rapid molecular diagnostics and targeted interventions in Jiangxi to address distinct DR-TB patterns and demographic disparities.



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PMID: 41164440

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**3. Tracking the evolution of an extensively drug-resistant cross-border Mycobacterium tuberculosis cluster, Europe, January 2016 up to August 2025: implications for European surveillance.**

Euro Surveill. 2025 Nov;30(46):2500838. doi: 10.2807/1560-7917.ES.2025.30.46.2500838.

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Milan, Italy.

The emergence and spread of an extensively drug-resistant (XDR) Mycobacterium tuberculosis lineage 4.8 cluster in Europe raises public health concerns. First reported in 2020 across Romania, Italy and the United Kingdom, this cluster progressed from multidrug-resistant (MDR) and pre-extensively drug-resistant (pre-XDR) to XDR, including resistance to pretomanid. Evidence of ongoing local transmission is available for Italy, where 10 cases were reported from 2021 to 2025. Strengthened whole genome sequencing-based surveillance is needed to inform timely, coordinated public health responses.

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**4. Differences in pulmonary nodular consolidation features among drug-sensitive pulmonary tuberculosis and multidrug/extensively-resistant pulmonary tuberculosis: a multi-national multi-center study.**

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BACKGROUND: Pulmonary nodular consolidation (PN) may represent an imaging sign potentially useful in differentiating multidrug-resistant (MDR) pulmonary tuberculosis (PTB) from drug-sensitive (DS) tuberculosis (TB) on chest computed tomography (CT). This study aims to confirm the difference in PN features between DS and MDR patients.
METHODS: Eastern European (Belarus, Moldova, Romania, Azerbaijan, and Georgia) patient data were obtained from the NIAID TB (National Institute of Allergy & Infectious Diseases Tuberculosis) Portals Program registered before January 2019. Chinese patients were obtained from Shenzhen, China, treated between April 2017 and February 2019. There were in total 244 DS cases (222 new patients and 22 previously treated patients), 344 MDR cases (188 new patients and 156 previously treated patients), 155 extensively drug-resistant (XDR) TB cases (36 new patients and 119 previously treated patients). The first CT scan's images were used. A PN was defined as rounded or oval with a relatively clear boundary measuring between 6 and 30 mm in diameter. Calcified lesions in the lungs, as a sign of chronicity, were also recorded.
RESULTS: In new patients, there was no difference in lung lesion calcification prevalence among DS (16.1%) and MDR (15.0%). In previously treated patients, lung calcification prevalence was 38.5% for DS, 48.3% for MDR, and 52.8% for XDR. For new patients, the PN prevalence was higher for MDR/XDR cases than for

DS cases (around 70% vs. around 39%). PN prevalence increased for DS cases from around 39% for new patients to 59% for treated patients, but the increases for MDR/XDR cases were minimal. For new patients, the mean PN number for positive cases was DS: 2.38, MDR: 2.89, XDR: 2.72. For treated cases, the mean PN number for positive cases was DS: 2.54, MDR: 3.91, XDR: 4.99. For both new patients and treated patients, PN No. ≥3 had a specificity of around 85% suggesting the diagnosis of XDR/XDR. The number of lung fields with PN lesion was higher for MDR cases than for DS cases. PN lesions were even more widely spread in XDR cases than in MDR cases. Additional analysis of recent literature suggests that a trend may exist in the frequency of lung lesions: DS < RR (rifampicin-resistant) < MDR < XDR.
CONCLUSIONS: MDR/XDR patients exhibit significantly higher PN prevalence and more extensive pulmonary involvement compared to DS patients and which is not totally determined by disease history length, suggesting that PN characteristics could serve as imaging biomarkers for drug resistance assessment.



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**5. Expanding diagnostic testing for drug-resistant tuberculosis in high burden settings: a cost-effectiveness analysis.**

BMC Public Health. 2025 Nov 5;25(1):3795. doi: 10.1186/s12889-025-24934-z.

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BACKGROUND: New and effective tools for detecting drug-resistant tuberculosis (DR-TB) include GeneXpert XDR and targeted Next Generation Sequencing (tNGS). However, data on their implementation in high TB-burden settings is limited. We aimed to determine cost-effectiveness of different strategies using GeneXpert XDR or tNGS for DR-TB detection in high TB-burden, low-resource settings.
METHODS: A dynamic simulation model was calibrated to WHO-reported TB data for Philippines and Thailand. Intervention scenarios for expanded diagnostic testing of drug-resistance were simulated for 2025 - 2035. Health benefits were estimated using disability-adjusted life years. Cost-effectiveness was calculated from a health system perspective using country-level TB diagnosis and treatment costs. Analyses include incremental cost-effectiveness ratios (ICERs) and incremental net monetary benefit (INMB).
RESULTS: Implementing GeneXpert XDR or tNGS for DR-TB detection improves TB health outcomes. Scenarios using GeneXpert XDR are more likely to be cost-effective than scenarios using tNGS. Interventions targeting previously treated cases reduce costs but also reduce health benefits. Testing all TB cases with GeneXpert XDR is cost-effective (Philippines ICER = $1,808, INMB = $210M; Thailand ICER = $5,251, INMB = $26M) with a 1 x GDP willingness-to-pay threshold (WTP). Targeting GeneXpert XDR to previously treated cases is also cost-effective (Philippines ICER = $1,288, INMB = $52M; Thailand ICER = $3,667, INMB = $9.2M) but results in lower INMB. tNGS is cost-effective at higher WTP.
INTERPRETATION: In high TB-burden countries, GeneXpert XDR is cost-effective as an additional DR-TB diagnostic test. tNGS is not cost-effective for routine clinical DR-TB testing but has potential for application to high-risk populations, especially with introduction of new TB treatment regimens.



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**6. Lefamulin harbors promising anti-tuberculosis activity against multidrug-resistant Mycobacterium tuberculosis isolates.**

Microbiol Spectr. 2025 Nov 4;13(11):e0225025. doi: 10.1128/spectrum.02250-25. Epub 2025 Oct 8.

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Multidrug-resistant tuberculosis (MDR-TB) is often associated with poor clinical outcomes. This study evaluated the in vitro activity of lefamulin (LEF) and intracellular activities against Mycobacterium tuberculosis. In this study, we evaluated the potential of LEF as a new drug candidate for treating M. tuberculosis infections, including MDR-TB. The antimicrobial susceptibility testing was performed to determine the minimum inhibitory concentrations (MICs) of LEF against 132 clinical isolates of M. tuberculosis. The intracellular activity of LEF and its interaction with other anti-tuberculosis drugs were also evaluated using M. tuberculosis H37Rv. From the 132 M. tuberculosis clinical isolates, the MIC50 and MIC90 were 0.5 µg/mL and 1 µg/mL, respectively. The tentative epidemiological cut-off (ECOFF) against LEF was defined at 1 µg/mL. After 5 days of incubation, LEF at 2 µg/mL inhibited 89.88% ± 1.73% of intracellular bacterial growth, which was comparable with the inhibitory rate of 94.29% ± 1.32% achieved by INH at 2 µg/mL. In addition, a synergy between LEF and bedaquiline (BDQ) was observed with a fractional inhibitory concentration index = 0.5. Furthermore, LEF showed no correlation with resistance to 10 anti-tuberculosis drugs. The minimum bactericidal concentration/MIC of LEF values suggested that it is a bacteriostatic drug against M. tuberculosis, and the bactericidal activity is mainly characterized by a concentration-dependent pattern. LEF has potent inhibitory activities against M. tuberculosis in vitro as well as in macrophages. Furthermore, the synergistic effect with BDQ also favors LEF as a promising drug candidate for tuberculosis treatment, especially for MDR-TB.IMPORTANCELefamulin (LEF), the first systemic pleuromutilin antibiotic approved for human use, exhibits broad-spectrum activity against Gram-positive bacteria. However, its in vitro activity against Mycobacterium tuberculosis (Mtb) remains unexplored. This study evaluated the potential of LEF

for treating Mtb infections, including multidrug-resistant tuberculosis. Our findings demonstrate that LEF possesses potent bacteriostatic activity against Mtb in vitro and exhibits synergistic effects when combined with bedaquiline. These results suggest LEF as a promising therapeutic candidate for tuberculosis treatment.

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PMID: 41059697 [Indexed for MEDLINE]

Conflict of interest statement: The authors declare no conflict of interest.

**7.Diagnostic assistance method for RR-TB/MDR-TB patients under treatment based on CNN-LSTM.**

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The rapid development of deep learning has promoted its application in disease diagnosis, treatment, and prognosis prediction. Medical imaging plays a crucial role in the management of rifampicin-resistant tuberculosis/multidrug-resistant tuberculosis (RR-TB/MDR-TB). In particular, chest computed tomography (CT) scans offer detailed lung images that can reveal subtle features. In this study, we propose a Convolutional Neural Network-Long Short-Term Memory (CNN-LSTM) model to predict treatment outcomes in RR-TB/MDR-TB patients, aiming to support clinicians in timely adjustment of therapeutic strategies and improving treatment success. The model integrates CNN for image feature extraction with LSTM for sequential analysis of patient monitoring data, including two types of immune detection indicators (T-cell subsets and peripheral blood tuberculosis-related CD161-positive cells). Transfer learning with weight initialization was applied to enhance model performance, and three backbone architectures (DenseNet201 + ABC, ResNet-50 + ABC, CheXNet + ABC) were compared to assess their impact on predictive accuracy. Experimental results demonstrated that the CNN-LSTM model with DenseNet201 + ABC as the backbone achieved the highest accuracy in predicting subsequent treatment indicators. These findings demonstrated the feasibility and effectiveness of using CNN-LSTM for treatment outcome prediction in RR-TB/MDR-TB, and highlighted its potential to assist clinicians in precision-tailoring treatment plans, thereby improving therapeutic efficacy and offering both theoretical and practical value in healthcare.



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PMID: 41168391 [Indexed for MEDLINE]

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**8. Overcoming Treatment Challenges in HIV-Associated Mycobacterial Diseases: New Therapeutic Frontiers.**

Int J Mol Sci. 2025 Oct 23;26(21):10325. doi: 10.3390/ijms262110325.

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For drug-susceptible TB, the WHO-endorsed first-line regimen (isoniazid, rifampicin, ethambutol, pyrazinamide) remains the global reference. Therapy must always be tailored to drug susceptibility, especially in MDR- and XDR-TB. HIV-associated mycobacterial infections-including Mycobacterium tuberculosis (TB), disseminated Mycobacterium avium complex (MAC), and Mycobacterium leprae (M. leprae)-remain leading causes of morbidity and mortality in people living with HIV (PLWH). TB continues to account for the highest burden of AIDS-related deaths worldwide, while MAC and leprosy complicate care in advanced immunosuppression. This review synthesizes current evidence on epidemiology, clinical features, and management challenges of HIV-mycobacterial co-infections. We discuss drug-susceptible and drug-resistant TB therapies, drug-drug interactions with antiretroviral therapy (ART), and the clinical impact of immune reconstitution inflammatory syndrome (IRIS). Beyond established regimens, we highlight host-directed strategies such as metformin, glutathione augmentation, mTOR modulation, and vitamin D; immunotherapies including interferon-γ, GM-CSF, and IL-7; and therapeutic vaccines (M72/AS01E, MTBVAC, VPM1002) as promising adjuncts. Distinct from guideline-focused overviews, this review emphasizes non-tuberculous mycobacterial disease (NTM, including MAC) and leprosy in PLWH and synthesizes host-directed and adjunctive strategies with their translational prospects, including ART compatibility and IRIS. By integrating TB, NTM, and leprosy across the HIV care continuum, we highlight opportunities not treated in detail elsewhere-particularly HDT-enabled approaches and implementation considerations in PLWH.

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PMCID: PMC12609301
PMID: 41226364 [Indexed for MEDLINE]

Conflict of interest statement: The authors declare no conflicts of interest.

**9.Synergistic Effects of Curcumin and Antibiotics Against Drug-Sensitive and Multidrug-Resistant Mycobacterium tuberculosis.**

Int J Mol Sci. 2025 Oct 27;26(21):10414. doi: 10.3390/ijms262110414.

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Tuberculosis (TB), caused by Mycobacterium tuberculosis (Mtb), remains a global health challenge, partly due to the prolonged duration and toxicity of standard antibiotic regimens. Adjunctive therapies that enhance antimicrobial efficacy and modulate host immunity are urgently needed. Curcumin, a natural bioactive compound derived from Curcuma longa, possesses broad therapeutic properties, including anti-inflammatory, antioxidant, antibacterial, and antiviral effects. This study evaluated the effects of curcumin in combination with first- and second-line antibiotics against Mtb in both in vitro and in vivo models. Our results demonstrated that curcumin exerts direct antibacterial activity against both the drug-sensitive H37Rv strain and a multidrug-resistant (MDR) clinical isolate. Furthermore, curcumin synergized with conventional antibiotics, enhancing bacterial clearance in infected macrophages while promoting the production of IL-12, a key cytokine in protective immune responses. In a murine model of progressive pulmonary TB, combination therapy with curcumin and first-line antibiotics significantly reduced the lung bacterial burden and improved behavioral outcomes compared to antibiotic treatment alone. These findings suggest that curcumin acts through both direct antimicrobial mechanisms and immune modulation, supporting its potential as an adjunctive therapy agent for TB. Future studies should focus on optimizing curcumin formulation, dosing, and bioavailability to facilitate the clinical translation of this compound.

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PMID: 41226452 [Indexed for MEDLINE]

Conflict of interest statement: The authors declare no conflicts of interest.

**10. Analysis of drug-resistant tuberculosis transmission dynamics in China using**

**fractional stochastic model.**

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This study investigates the dynamics of the drug-resistant tuberculosis model through a fractional stochastic modeling framework. The model employs fractional-order derivatives to capture the memory effects in disease transmission, while Brownian motion is introduced to represent the random disturbances, thereby providing a more realistic description of the disease dynamics. First, a fractional deterministic model based on the Atangana-Baleanu-Caputo derivative was developed, and its optimal parameter values were obtained from the actual data from the case of drug-resistant tuberculosis in China. Second, the existence and uniqueness of the solution of the fractional stochastic model were proved, and its numerical solution was explored. Furthermore, the impacts of different interventions strategies on the control of drug-resistant tuberculosis in China were compared. The results demonstrate that the combined interventions exhibit superior efficacy compared to any single intervention. Numerical simulations of deterministic and fractional stochastic models verify the effects of memory and random effects on drug-resistant tuberculosis. It was found that as the noise level increases, the degree of random perturbation in the model solution also increases, and higher noise levels may lead to the early disappearance of drug-resistant tuberculosis.



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**11. Scaffold Hopping in Tuberculosis Drug Discovery: Principles, Applications, and Case Studies.**

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Tuberculosis (TB) imposes a major global health challenge, aggravated by the emergence of drug-resistant Mycobacterium tuberculosis (Mtb) strains. Scaffold hopping, a medicinal chemistry approach that modifies the molecular backbone of known bioactive compounds, has emerged as a promising tool in the development of novel drugs, including TB therapeutics. This perspective provides an insight into the application of scaffold hopping across varying degrees of structural modifications, highlighting successful case studies targeting key Mtb pathways, including energy metabolism, cell wall synthesis, proteasome function, and respiratory processes. Beyond traditional and in silico methods, scaffold hopping has spurred the discovery of compounds with improved pharmacological profiles, such as improved pharmacokinetics, enhanced efficacy, reduced toxicity, and resistance circumvention. The findings support scaffold hopping's potential to address the limitations of current anti-TB drugs as a versatile and innovative approach to accelerate TB drug discovery.

DOI: 10.1021/acs.jmedchem.5c01100
PMCID: PMC12557394
PMID: 41055946 [Indexed for MEDLINE]

**12. Predictive Factors Associated With Multidrug-Resistant Tuberculosis Among Tuberculosis Patients in Southwest Ethiopia: An Unmatched Case-Control Study.**

Health Sci Rep. 2025 Oct 28;8(11):e71408. doi: 10.1002/hsr2.71408. eCollection 2025 Nov.

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BACKGROUND: Multidrug-resistant tuberculosis (MDR-TB) presents a significant public health challenge, particularly in resource-limited settings like Ethiopia. Identifying factors associated with MDR-TB is essential for designing effective control strategies. The objective of this study was to identify the determinants of multidrug-resistant tuberculosis (MDR-TB) in southwest Ethiopia, to inform targeted public health interventions, improve prevention and control strategies, and support evidence-based planning in regions with limited resources and a high burden of drug-resistant TB.
METHODS: An unmatched case-control study was conducted from October 2022 to February 2023 in Jimma and Illubabor zones, located in Southwest Ethiopia. A total of 201 participants were initially selected, of whom 200 (66 MDR-TB cases and 134 drug-susceptible TB controls) completed the study and were included in the final analysis. Data were collected through interviewer-administered questionnaires and review of medical records. Variables with a p-value < 0.25 in bivariable analysis were entered into multivariable logistic regression to identify independent predictors of MDR-TB. Adjusted odds ratios (AORs) with 95% confidence intervals (CIs) were used, and statistical significance was declared at $p < 0.05$.
RESULTS: Among the 200 participants included, several factors were significantly associated with MDR-TB. Compared to those aged 15-24 years, participants aged 25-34 years (AOR = 3.8, 95% CI: 1.34-8.36) and 35-44 years (AOR = 3.3, 95% CI: 1.42-7.65) had higher odds of MDR-TB. Other significant predictors included urban residence (AOR = 2.1), contact with TB or known MDR-TB patients (AOR = 2.21), HIV infection (AOR = 1.9), substance use (alcohol, khat, illicit drugs), psychological illness (AOR = 9.4), previous TB treatment (AOR = 5.3), retreatment history (AOR = 13.9), low BMI (< 18.5 kg/m²; AOR = 3.9), living more than 25 km from treatment centers (AOR = 6.2), and perceived social stigma (AOR = 5.2).
CONCLUSION: This study identified multiple independent predictors of MDR-TB, including previous TB treatment, retreatment history, substance use, HIV infection, psychological illness, malnutrition, and limited access to healthcare. Sociodemographic factors such as age, urban residence, and perceived stigma were also significant. These findings highlight the need for integrated TB control strategies addressing clinical management, behavioral and psychosocial support, and improved healthcare access to effectively reduce MDR-TB in Southwest Ethiopia.

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PMCID: PMC12559812
PMID: 41163939

Conflict of interest statement: The authors declare no conflicts of interest.

**13. Whole-lung computed tomography radiomics combined with clinical features for differentiating multidrug-resistant tuberculosis from drug-sensitive tuberculosis: a retrospective multi-center study.**

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BACKGROUND: Multidrug-resistant tuberculosis (MDR-TB) poses an escalating public health challenge that complicates diagnosis and treatment. Early detection is crucial for improving the outcomes. This study aimed to evaluate the diagnostic performance of whole-lung computed tomography (CT) radiomics features combined with clinical characteristics in distinguishing MDR-TB from drug-sensitive tuberculosis (DS-TB).
METHODS: This retrospective study included 750 patients with MDR-TB and DS-TB from two hospitals. Clinical data and non-contrast CT images were obtained. The radiomic features were extracted using PyRadiomics. A three-step feature selection process, including t-tests/U-tests, Pearson correlation, and the least absolute shrinkage and selection operator (LASSO), was employed to identify the optimal features. Diagnostic models based on clinical and radiomic features were constructed using LightGBM and multilayer perceptron (MLP) algorithms, respectively. A combined model integrated both types of features. Model

performance was assessed using area under the curve (AUC), accuracy, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and F1 score.
RESULTS: Diabetes mellitus and tuberculosis (TB) retreatment were identified as independent risk factors for MDR-TB. The clinical model achieved AUC values of 0.742, 0.738, and 0.725 for training, internal validation, and external validation sets, respectively. Seven radiomics features were selected, with the radiomics model achieving AUC values of 0.724, 0.720, and 0.703. The combined model outperformed the individual models, with AUC values of 0.816, 0.795, and 0.835, and superior sensitivity and specificity.
CONCLUSIONS: Integrating whole-lung CT radiomics with clinical features significantly enhances the diagnostic accuracy of MDR-TB. The combined model outperforms individual models, underscoring the potential of radiomic-clinical data integration. This approach could expand MDR-TB screening coverage without additional economic burden, thereby facilitating prevention and control.



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PMID: 41229755

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**14. Key resistance-associated mutations in multidrug-resistant tuberculosis: a genomic study from Shanghai, China, with a focus on aminoglycosides.**

BMC Microbiol. 2025 Oct 30;25(1):702. doi: 10.1186/s12866-025-04446-x.

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The aminoglycosides are essential drugs in the treatment of multidrug-resistant

tuberculosis. Antibiotic resistance of Mycobacterium tuberculosis is a major public health concern worldwide. Therefore, it is of great significance to characterize the mutations by which susceptible M. tuberculosis evolves into drug resistance. A total of 110 clinical isolates of MDR-TB were used for Whole-genome sequencing (WGS) and phenotypic drug susceptibility testing to aminoglycosides, including amikacin, kanamycin, and streptomycin. Among 110 clinical MDR-TB strains, 7 (6.36%) were cross-resistant to amikacin and kanamycin, and 81 (73.64%) were resistant to streptomycin. The resistance rates to rifabutin, streptomycin, moxifloxacin, ofloxacin, and ethambutol were observed in 79.09%, 73.64%,35.45%, 34.55%, and 30.91%, respectively. Among the 81 MDR-TB strains resistant to streptomycin, the MIC values of streptomycin against MDR-TB showed the following distribution: 61 strains (75.31%) demonstrated resistance with MICs ≥ 32 μg/ml. The rrs gene mutations were detected in 6 (85.71%; 6/7) of the amikacin/kanamycin-resistant isolates, with the most frequent mutation being A1401G. Mutations in the eis promoter were identified at two positions in 3 amikacin/kanamycin-susceptible and streptomycin-resistant isolates (-10G > A and - 37G > T). In 80.25% (65 out of 81) of streptomycin-resistant MDR-TB isolates, two types of amino acid substitutions associated with rpsL mutations were identified. K43R was observed in 86.15% of isolates with mutations in rpsL, followed by K88R at 13.85%. In conclusion, current critical concentration methods and the design of molecular diagnostics need to be revisited to provide more accurate assessments of streptomycin resistance for rspL mutation-bearing isolates.



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PMID: 41168684 [Indexed for MEDLINE]

Conflict of interest statement: Declarations. Ethics approval and consent to participate: This study received approval from the Ethical Committee of Shanghai Pulmonary Hospital. Informed consent was obtained from all participants involved in the study. This research complied with the Declaration of Helsinki. Consent for publication: Not Applicable. Competing interests: The authors declare no competing interests.

**15. Development and evaluation of the phenotypic 2G test to detect drug-resistant TB.**

IJTLD Open. 2025 Nov 12;2(11):685-691. doi: 10.5588/ijtldopen.25.0326. eCollection 2025 Nov.

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BACKGROUND: Early diagnosis of TB with drug susceptibility testing (DST) is critical to achieve successful treatment outcomes. We aimed to develop and test a novel colorimetric, 12-well, thin-layer agar-based test to assess its accuracy for TB diagnosis and DST in a clinical setting in Southern Mozambique.
METHODS: Development of the first prototype of the second generation (2G) test in the laboratory setting followed by a cross-sectional diagnostic accuracy study with consecutive recruitment of subjects with microbiologically confirmed TB using GeneXpert MTB/RIF Ultra.
RESULTS: In the laboratory setting, the 2G test showed 100% accuracy in detecting resistance of genotypically characterised drug-resistant Mycobacterium tuberculosis strains. In the clinical setting, the sensitivity of the 2G test to detect M.tb complex versus Xpert and Mycobacteria Growth Indicator Tube (MGIT) culture using fresh sputa was 45.9% and 45.2%, respectively. The 2G test sensitivity versus MGIT decreased to 23.1% when using frozen decontaminated sputum samples.

CONCLUSION: In the clinical setting, the 2G test showed a low sensitivity versus Xpert and MGIT. The 2G test sensitivity was lower when frozen instead of fresh sputa was used. Despite these results, important information was collected to further improve this 2G test prototype and its implementation in resource-constrained settings.



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PMID: 41246467

Conflict of interest statement: Conflict of interest: none declared.

**16. Deriving Dosages for Levofloxacin Tuberculosis Preventive Treatment for Young People Exposed to Rifampicin-Resistant Tuberculosis.**

J Infect Dis. 2025 Nov 14;232(5):1178-1186. doi: 10.1093/infdis/jiaf401.

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BACKGROUND: Tuberculosis (TB) is the leading single bacterial cause of death worldwide. In 2023, approximately 400 000 people developed multidrug- and rifampicin-resistant TB (MDR/RR-TB), which complicates treatment. TB preventive treatment (TPT) is a critical strategy to prevent the progression from TB infection to TB disease among those at risk. In February 2024, based on data from 2 randomized controlled trials, levofloxacin was strongly recommended by the World Health Organization (WHO) as a TPT option in people of all ages exposed to MDR/RR-TB. There are uncertainties about the optimal dosing of levofloxacin in children and adolescents when using dispersible and solid

formulations. We used pharmacokinetic modeling and simulations to determine the best dosing strategy in people aged up to 19 years for both formulations of levofloxacin.
METHODS: A previously developed population pharmacokinetic model of levofloxacin in children (0.2-16.8 years) was used and applied to new WHO harmonized weight bands. Simulations were conducted using demographic data from countries with the highest incidence of RR- or MDR-TB. Two currently available levofloxacin formulations (100 mg pediatric, dispersible tablets and 250 mg solid tablets) were considered.
RESULTS: A dosing regimen by weight band was developed for levofloxacin when used as TPT in people aged 0-19 years exposed to MDR/RR-TB. Doses correspond to 8-33 mg/kg for the 100 mg dispersible tablets and 10-42 mg/kg for 250 mg solid tablets. These doses achieve adequate adult target exposure levels.
CONCLUSIONS: Pragmatic, weight-band dosing strategies help simplify the administration of MDR/RR-TB TPT and have been included in WHO guidance.



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PMID: 40794705 [Indexed for MEDLINE]

Conflict of interest statement: Potential conflicts of interest. All authors: No reported conflicts of interest.

**17. Plasma and CSF pharmacokinetic characteristics of second-line anti-tuberculosis drugs in a patient with multidrug-resistant tuberculous meningitis.**

BMC Infect Dis. 2025 Nov 21;25(1):1632. doi: 10.1186/s12879-025-12052-5.

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BACKGROUND: The treatment of multidrug-resistant tuberculous meningitis (MDR-TBM) presents significant challenges, as the ability of different anti-tuberculosis (anti-TB) drugs to penetrate the blood-brain barrier varies greatly. The pharmacokinetic characteristics of second-line anti-TB drugs including bedaquiline, cycloserine, moxifloxacin and contezolid remains unclear, particularly in cerebrospinal fluid (CSF).
CASE PRESENTATION: We report a case of a 30-year-old female who was diagnosed with MDR-TBM. Therapeutic drug monitoring (TDM) was used to determine whether each anti-TB drug's peak concentration reached the effective range, and concentrations of each anti-TB drug in plasma and CSF of the patient after 5, 7, 9 and 12 h of medication was detected, the CSF/plasma concentration ratio of each anti-TB drug was also analyzed.
CONCLUSIONS: TDM plays an important role in clinical individualized medication adjustment. Cycloserine, pyrazinamide, contezolid and moxifloxacin may have a high CSF permeability. This study provided valuable reference for the clinical management of MDR-TBM by measuring the plasma and CSF concentrations of anti-TB drugs.

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PMCID: PMC12639686
PMID: 41272543

Conflict of interest statement: Declarations. Ethics approval and consent to participate: This study was approved by the Ethics Committee of Zhejiang Hospital of Integrated Traditional Chinese and Western Medicine. Institutional approval for the publication of anonymized clinical details was obtained from Zhejiang Hospital of Integrated Traditional Chinese and Western Medicine in accordance with local regulations and ethical guidelines. Consent for publication: Written informed consent was obtained from the patient's parents for publication of this case report and accompanying statistics. Identifying information has been anonymized. Competing interests: The authors declare no competing interests.

**18. Targeted next-generation sequencing for drug-resistant tuberculosis diagnosis: implementation considerations for bacterial load, regimen selection and diagnostic algorithm placement.**

BMJ Glob Health. 2025 Nov 4;10(11):e019135. doi: 10.1136/bmjgh-2025-019135.

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INTRODUCTION: Early and accurate diagnosis of drug-resistant tuberculosis (DR-TB) is essential for improving treatment outcomes. Phenotypic drug susceptibility testing (pDST) is comprehensive but slow, while rapid molecular assays provide resistance information for a limited number of drugs. Targeted next-generation sequencing (tNGS) offers the potential for broad and rapid resistance detection, but its integration into diagnostic algorithms has been hindered by uncertainty about its placement within existing workflows.
METHODS: This study evaluated the extent to which two tNGS solutions-Deeplex Myc-TB (GenoScreen) and TB Drug Resistance Test (Oxford Nanopore Technologies, ONT)-provided interpretable drug resistance results that could inform regimen design, in comparison to other WHO-recommended molecular assays and pDST. Data were collected from three high-burden DR-TB settings under the Seq&Treat study. Sequencing success rates and drug resistance detection were analysed based on: (1) the initial Xpert MTB/RIF result (very low, low, medium, high), (2) resistance results for drugs in WHO-recommended regimens and (3) performance relative to other WHO-endorsed assays. The potential impact of different algorithms on the estimates was also considered. Key factors influencing successful tNGS adoption within diagnostic pathways were identified, leveraging insights from the Seq&Treat diagnostic accuracy study.
RESULTS: Sequencing success rates were 88.5% (GenoScreen) and 93.1% (ONT) across 763 samples. While tNGS provided complete resistance data for 73%-86% of drugs in recommended regimens, pDST achieved 92%-93%. Both tNGS solutions matched or exceeded the sensitivity of WHO-recommended molecular assays.
CONCLUSIONS: This study highlights the critical role of tNGS as a centralised tool for comprehensive drug resistance testing to inform DR-TB treatment

decisions following initial screening assays. By complementing existing molecular tests with tNGS, diagnostic workflows can be optimised to ensure timely and comprehensive resistance detection. These findings support policy updates to integrate tNGS into global TB diagnostic algorithms.
TRIAL REGISTRATION NUMBER: NCT04239326.



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PMCID: PMC12588000
PMID: 41192929 [Indexed for MEDLINE]

Conflict of interest statement: Competing interests: REC received salary support and travel cost reimbursement according to the terms of a service contract between FIND and their home institution, UC San Diego. REC has additionally received funding for a grant through NIH/NIAID to develop and evaluate a tNGS solution for drug resistant TB (R01AI176401). REC is a co-inventor on a patent associated with the processing of TB sequencing data (European Patent Application number 14840432.0 & USSN 14/912,918). REC has agreed to 'donate all present and future interest in and rights to royalties from this patent' to Translational Genomics Research Institute.

**19. Bedaquiline Resistance and Treatment Outcomes Among Patients With Tuberculosis Previously Exposed to Bedaquiline in India: A Multicentric Retrospective Cohort Study.**

Clin Infect Dis. 2025 Nov 6;81(4):846-852. doi: 10.1093/cid/ciaf068.

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Erratum in
Clin Infect Dis. 2025 Jun 4;80(5):e79. doi: 10.1093/cid/ciaf174.

BACKGROUND: Bedaquiline (BDQ) resistance presents a critical challenge in the fight against tuberculosis (TB), particularly multidrug-resistant (MDR) strains. The emergence of resistance to BDQ, a key drug in treating MDR-TB, poses significant threats to TB treatment effectiveness.
METHODS: The National Institute of Tuberculosis and Respiratory Diseases in Delhi and the Médecins Sans Frontières clinic in Mumbai provide BDQ, delamanid, and carbapenem-based regimens for patients with suspected or confirmed treatment failure. BDQ phenotypic drug-susceptibility testing (DST) was performed for all BDQ-exposed patients. Treatment regimens were individualized based on exposure history, comorbidities, drug interactions, prior adverse drug reactions, and DST results.
RESULTS: Of 117 BDQ-exposed patients from December 2020-December 2022, 42 (36%) exhibited a BDQ-resistant strain. Median (IQR) age was 24 (22-32) years, with 63 (54%) females and 94% with pulmonary TB. Patients with a BDQ-resistant strain were older (median age: 27 vs 23 years; P = .04), more likely to have lung cavities (risk ratio [RR]: 1.8; 95%-CI: 1.1-3.1; P = .02), and be resistant to clofazimine (RR: 2.3; 95%-CI: 1.5-3.6; P = .001). Overall, 102 patients initiated treatment. Patients with BDQ-resistance had higher risk of unfavorable outcomes compared with BDQ-susceptible patients (RR:2.1; 95%-CI: 1.5-2.8; P < .001). Overall, 87% (33/38) of patients with BDQ-resistance experienced unfavorable treatment outcomes: 15 (40%) died, 15 (40%) had treatment failure, and 3 (8%) were lost-to-follow-up.
CONCLUSIONS: The study highlights a concerning rate of BDQ-resistance among previously treated patients, resulting in poor treatment outcomes. To prevent treatment failure, we recommend implementing BDQ-DST, developing affordable and accurate rapid tests for BDQ-resistance, and intensifying research and development efforts for newer TB drugs.



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PMCID: PMC12596394
PMID: 40079698 [Indexed for MEDLINE]

**20. Global burden of HIV and drug-resistant tuberculosis co-infection and its attributable risk factors, 1990 to 2021, with projections to 2031.**

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BACKGROUND: The persistent global spread of HIV and drug-resistant tuberculosis (HIV/DR-TB) co-infection poses a significant challenge to international tuberculosis control efforts. This study aimed to analyze the global burden of HIV/DR-TB co-infection across age groups, genders, and Socio-demographic Index (SDI) regions, while identifying attributable risk factors.
METHODS: Data from the Global Burden of Disease (GBD) 2021 and joinpoint regression analysis were utilized to examine epidemiological trends from 1990 to 2021 across different genders and SDI regions. The Bayesian Age-Period-Cohort (BAPC) model was employed to forecast trends up to 2031.
RESULTS: HIV and multidrug-resistant tuberculosis (HIV/MDR-TB) co-infection exhibited no significant gender differences in prevalence, incidence, mortality, or DALYs (P = 0.053, 0.277, 0.354, 0.212). In contrast, HIV and extensively drug-resistant tuberculosis (HIV/XDR-TB) co-infection showed significantly higher rates in males for all outcomes (P = 0.007, 0.003, 0.003, 0.005). Burden distribution varied by SDI quintile: Low SDI bore a greater HIV/MDR-TB co-infection burden. High-middle SDI had higher HIV/XDR-TB co-infection prevalence. Unsafe sex was the predominant risk factor for HIV/DR-TB co-infections in both genders, followed by drug use in males and intimate partner violence in females. Regional risk patterns revealed that male drug use was more strongly associated with HIV/DR-TB co-infection in high-middle SDI regions, whereas unsafe sex and intimate partner violence (in females) showed greater impact in low SDI regions. Projections indicated a steady decline in HIV/DR-TB co-infection from 2021 to 2031.
CONCLUSION: Despite observed declines, HIV/DR-TB co-infection continues to pose a significant public health challenge. Regional SDI-stratified interventions are

urgently needed: low-SDI settings should prioritize healthcare system strengthening to address gender-specific vulnerabilities including unsafe sexual practices and intimate partner violence, while high-middle SDI regions require comprehensive drug abuse prevention programs combining public education with enhanced pharmaceutical controls.



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Conflict of interest statement: Declarations. Ethics approval and consent to participate: As it utilized publicly accessible secondary data which were anonymized and compiled, the need for informed Consent was waived for this research. The authors confirm that there are no competing interests to disclose. Consent for publication: Not applicable. Competing interests: The authors declare no competing interests.

**21. Trends and treatment outcomes of drug resistant tuberculosis in Limpopo Province, South Africa (2011-2019): A Retrospective Study.**

PLoS One. 2025 Nov 18;20(11):e0335600. doi: 10.1371/journal.pone.0335600. eCollection 2025.

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BACKGROUND: Drug-resistant tuberculosis (DR-TB) continues to threaten TB control efforts in South Africa, particularly in resource-limited provinces such as Limpopo. This study evaluated trends in DR-TB and evaluated treatment outcomes and predictors of unfavorable outcomes from 2011 to 2019.
METHODS: We conducted a retrospective cross-sectional study using data from 3,528 patients with DR-TB recorded in the Limpopo electronic registry (EDRWeb.net). Descriptive statistics characterized the demographics of the patients and the types of resistance. The associations between variables and outcomes were tested using chi-square analysis and binary logistic regression

identified independent predictors of unfavorable treatment outcomes. The study period was stratified into pre-bedaquiline (BDQ) (2011-2015) and post-BDQ (2016-2019) eras to assess the impact of treatment.
RESULTS: Rifampicin-resistant TB (RR-TB) (61.7%) and multidrug-resistant TB (MDR-TB) (32.5%) were the most common. Overall, the success of the treatment was 59.0%, increasing from 54.1% in the pre-BDQ era to 65.3% after BDQ. XDR-TB had the lowest success rate (31.3%). In multivariate analysis, male sex (aOR = 1.12; 95% CI: 1.00-1.27), HIV positivity (aOR = 1.28; 95% CI: 1.11-1.47), age ≥ 35 years (aOR = 2.01; 95% CI: 1.08-3.76), and XDR-TB (aOR = 3.05; 95% CI: 1.65-5.65) were independently associated with unfavorable outcome.
CONCLUSION: Treatment outcomes for DR-TB in Limpopo improved following the introduction of BDQ and shorter all-oral regimens but remain suboptimal, particularly among XDR-TB and HIV co-infected patients. Strengthening TB/HIV integration, expanding access to new drug regimens, and enhancing early diagnosis are essential to improve outcomes in rural high-burden settings.



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PMID: 41252432 [Indexed for MEDLINE]

Conflict of interest statement: No competing interests.

**22. Incidence and associated risk factors of anti-tuberculosis drug induced liver injury among TB patients.**

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BACKGROUND: Tuberculosis (TB) is a global health challenge. Use of anti-TB drugs to treat TB is associated with high prevalence of side effects that include anti-TB drug induced liver injury (ATDILI). The aim of this study was to determine the incidence and associated clinical risk factors of ATDILI among South African patients on treatment for TB disease.
METHODS: This was an ambispective case-control study of patients on treatment for TB disease receiving drug sensitive and drug resistant treatment regimens. The retrospective and prospective studies were done from January 2021 to June 2024, involving a total of 610 patients on treatment for TB disease from whom 13 had ATDILI. From the retrospective and prospective cohorts, we extracted 13 ATDILI cases and 276 controls. Additionally, 44 severe ATDILI cases were directly recruited from the hospital to enrich the number of cases in the study. Prospective patients were followed for up to 6 months, while retrospective participants had a single visit with follow-up durations determined by their parent studies. Logistic regression analysis was performed to identify clinical and demographic factors associated with the development of ATDILI).
RESULTS: In the studied cohorts, the incidence of ATDILI was 2.1% (13/610). The ATDILI cases and controls consisted of 215 (64.6%) male patients; 57 patients were diagnosed with hepatotoxicity, 44 from the hospitalized cohort,12 from the retrospective cohort and 1 patient from the prospective cohort. The median time from the initiation of treatment to the onset of hepatotoxicity was approximately 30 days. Univariate logistic regression revealed significant differences ($p < 0.05$) in sex ($p = 0.003$), HIV status ($p = 0.002$), BMI ($p = 0.038$), hypertension ($p = 0.047$) smoking ($p = 0.006$), and alcohol consumption ($p = 0.001$) in relation to ATDILI. Multivariate analysis further revealed that female sex ($p = 0.041$), HIV status (0.022) and alcohol consumption (0.048) were independently associated with an increased risk of ATDILI.

CONCLUSIONS: The incidence of ATDILI in this study was 2.1%, lower than the previously reported range of 3–36% and highlights the need for standardized definitions of phenotypes across studies. In univariable analysis, female sex, HIV status, BMI, hypertension, smoking, and alcohol consumption were identified as potential risk factors for ATDILI. Among these, multivariable analysis suggested that female sex, HIV status and alcohol consumption were associated with an increased risk of developing ATDILI.
SUPPLEMENTARY INFORMATION: The online version contains supplementary material available at 10.1186/s12879-025-11796-4.

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PMID: 41137008

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**23. The Effectiveness and Safety of Bedaquiline, Pretomanid, and Linezolid (BPaL)-Based Regimens for Rifampicin-Resistant Tuberculosis in Non-Trial Settings-A Prospective Cohort Study in Belarus and Uzbekistan.**

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BACKGROUND: Only 63% of patients initiating multidrug-resistant/rifampicin-resistant tuberculosis (MDR/RR-TB) treatment in 2020 were treated successfully. 24-Week all-oral bedaquiline, pretomanid, and linezolid (BPaL)-based regimens have demonstrated higher rates of treatment success and have been recommended by the World Health Organization. Operational research is urgently required to evaluate these regimens in non-trial settings.
METHODS: This was a prospective cohort study of patients with microbiologically confirmed MDR/RR-TB and pre-extensively drug-resistant TB (pre-XDR-TB) initiated on BPaL-based regimens in Belarus and Uzbekistan (February 2022-June 2023). All clinical care and research procedures were delivered by treating physicians. After treatment completion, patients were followed up at 6 and 12 months, including collecting sputum to ascertain recurrence. The primary objective was to estimate the effectiveness (cured or treatment completed) and safety (the occurrence of serious adverse events) of BPaL-based regimens.
RESULTS: A total of 677 patients initiated treatment with BPaL-based regimens during the study. We documented successful treatment outcomes in 95.3% (427/448) of patients with MDR/RR-TB treated with BPaL plus moxifloxacin and 90.4% (207/229) of patients with pre-XDR-TB treated with BPaL plus clofazimine. 10.2% (69/677) experienced serious adverse events including 24 deaths (3.5%), 11 of which occurred during treatment. 83.3% (20/24) of deaths were not related to TB or TB treatment. Of patients who were successfully treated and completed 12-month follow-up, 0.5% (2/383) had recurrence.
CONCLUSIONS: BPaL-based regimens for MDR/RR-TB and pre-XDR-TB are safe and highly effective in non-trial settings. These regimens should be considered for widespread implementation globally, and further research is needed to evaluate their performance in other key populations.



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**24. Genomic characterization of XDR Mycobacterium tuberculosis isolates in Argentina (2006-2015).**

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BACKGROUND: Tuberculosis (TB), caused by the intracellular bacterium Mycobacterium tuberculosis complex (Mtbc), remains a significant global health challenge, with Mtbc once again being the leading infectious killer worldwide. Despite over a century of research, the disease continues to pose a major threat, with an estimated one-fourth of the global population latently infected.

According to the World Health Organization (WHO), approximately 1.3 million deaths were attributed to TB in 2024 alone. The emergence of multidrug-resistant (MDR) strains, resistant to isoniazid and rifampicin, and extensively drug-resistant (XDR) strains, resistant to rifampicin (and may also be resistant to isoniazid), to at least one fluoroquinolone (levofloxacin or moxifloxacin) and to at least one other Group A drug (bedaquiline or linezolid), further complicates the situation, posing significant challenges for healthcare systems. While the WHO definition of XDR-TB has recently been updated, in this study we applied the classification in effect during the 2006-2015 period, when the isolates were collected and characterized. In Argentina, TB burden is moderate compared to other countries, with approximately 10,500 new cases and 1,000 deaths reported annually. While standard therapy is generally effective, XDR Mtb infections require prolonged and costly treatment and are often associated with a guarded prognosis.
METHODS: In this work, we applied whole-genome sequencing analysis to characterise XDR-TB strains circulating in Argentina between 2006 and 2015. Genotypic variants of each isolate were compared against resistance-associated variant databases and subjected to local and global phylogenetic analyses.
RESULTS: The analysis revealed no common origins for the most frequently observed resistance mutations. Notable variants associated with resistance to first-line drugs included katG Ser315Thr and fabG1 -15C < T for isoniazid, rpoB Ser450Leu and Asp435Val for rifampin, embB Gly406Ala, and Met306Ile for ethambutol, as well as multiple variants in the pncA gene linked to pyrazinamide resistance.
CONCLUSIONS: This study provides valuable insights into the molecular mechanisms of antibiotic resistance in M. tuberculosis, specifically focusing on XDR strains circulating in Argentina. The findings highlight the genetic diversity and complexity of resistance-associated variants, emphasizing the need for continued research and surveillance efforts to address this pressing global health threat.
CLINICAL TRIAL NUMBER: Not applicable.



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**25. The quantity and severity of adverse drug reactions experienced by patients with multi-drug resistant tuberculosis in the Ugu District.**

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MDR-TB treatment has a history of being associated with a lengthy regimen accompanied by numerous adverse drug reactions (ADRs). This notion results from the aminoglycoside-based regimen and its association with severe and long-term ADRs such as ototoxicity, renal impairment, and optic neuritis. The introduction of a shorter regimen offered a more convenient and safer regimen. Data on the safety of the short bedaquiline regimen (SBR) has rarely been explored since the widespread use of bedaquiline was recommended in 2018. This is especially important for a country like South Africa, where the factors influencing therapy outcomes are vast and multifactorial. The method employed in this study included an investigation of patient clinical charts and documentation of noted ADRs. This was deemed the most appropriate method because medical officers or doctors did not complete other data sources such as ADR reports. All patients from a three-year period diagnosed with MDR-TB were included in the study. The most documented ADRs were thrombocytopenia, hypothyroidism, prolonged QTc, gastrointestinal disturbances, and rash. Three of the 5 most common ADRs were categorized as severe. There were no ADR reports submitted for escalation to relevant authorities. New drugs to the MDR-TB regimen, bedaquiline, and linezolid were primarily responsible for most ADRs. SBR appears to be associated with more severe ADRs than initially anticipated or documented. The focus previously was on QTc prolongation. The cost, including financial, human and emotional on treating the ADRs should also be factored in when comparing to previous regimens. Based on current data, increased monitoring of baseline results and management time of ADRs is imperative in ensuring a better response to therapy. Established pharmacovigilance systems are necessary to ensure the continued safety of drugs, irrespective of the disease state or known safety profile of the drug.



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**26. Screening and targeted sequencing of stool for microbiologic confirmation and drug resistance determination in paucibacillary tuberculosis.**

PLOS Glob Public Health. 2025 Nov 21;5(11):e0005243. doi: 10.1371/journal.pgph.0005243. eCollection 2025.

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In 2023, an estimated 10.8 million people developed tuberculosis, and 1.25 million people died from this disease, including 161,000 deaths in people with HIV (PWH) in whom tuberculosis remains the leading cause of death. Detecting Mycobacterium tuberculosis drug resistance remains a challenge among patients with paucibacillary tuberculosis; since there is such low bacterial load in

their sputum it's unable to be detected via microscopy, there is also not enough bacteria for other sputum-based tests which could provide resistance testing. At an outpatient clinic in Eswatini from 2020-2023, stool and sputum samples were provided by a subset of children, adolescents, and adults prospectively enrolled in a tuberculosis diagnostic study. In addition to standard diagnostic testing available in country (direct sputum Xpert, stool Xpert, and phenotypic drug susceptibility testing of sputum culture), stool samples underwent extraction and sequencing using targeted next generation sequencing (tNGS), using both the Oxford Nanopore Technologies (ONT) TB Custom Kit (on an ONT MinION Mk1b) and the Deeplex Myc-TB kit (on an Illumina iSeq 100). From 250 participants with pulmonary tuberculosis diagnosed in Eswatini during our study period, 85 (34%) were smear negative on sputum microscopy. Of these, 21/85 (24.7%) participants had adequate M. tuberculosis DNA shed in their stool for attempting tNGS. Targeted sequencing on stool detected M. tuberculosis DNA in 14-19% (n = 12/85-16/85) and provided a full report of mutations associated with drug resistance in 12-14% (n = 10/85-12/85) of patients with paucibacillary (smear-negative) tuberculosis, expanding drug resistance detection beyond other methods. Targeted sequencing of stool, even when applied to patients with paucibacillary disease, can provide case confirmation and expanded drug resistance information.



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**27. Rapid screening of mutations for second-line-drug-resistant genes in Mycobacterium tuberculosis culture isolates by in-house developed DNA bio-chip.**

Eur J Clin Microbiol Infect Dis. 2025 Nov;44(11):2645-2654. doi: 10.1007/s10096-025-05221-6. Epub 2025 Jul 29.

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BACKGROUND: The rate of multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis (TB) has been steadily increasing and is a major setback to TB control in India. The availability of quick and reliable methods for detecting second-line drug resistance (SLDR) is vital to managing patients satisfactorily. A rapid molecular technique to detect SLDR in Mycobacterium tuberculosis (M. tuberculosis) has been developed using DNA biochip.
METHODS: Specific probes containing wild-type region or specific mutations were designed for immobilization on DNA bio-chip. DNA bio-chip was developed in-house on polycarbonate track-etched membranes (PC-TEM). DNA bio-chip allows the identification of mutations in gyrA gene for fluoroquinolone (FQ) resistance, in rrs gene and the eis promoter region for resistance to second-line injectable drugs (SLID). An asymmetric multiplex PCR was standardized for gyrA, rrs and eis genes. A chemiluminescence based biochip assay was optimized. Bio-chip was tested on 112 M. tuberculosis clinical isolates with different resistance spectra.
RESULTS: Isolates analyzed using bio-chip shows that 61 (61%) samples were wild-type. Twelve samples show mutations in gyrA gene, 11 samples in rrs gene, 12 samples in eis gene and 4 samples show double mutation in rrs and eis genes. The sensitivity and specificity of bio-chip for detection of FQ resistance ranged from 75 to 100% and 96.7%-100%, respectively. The sensitivity and specificity of SLID detection ranged from 90.9 to 100% and 96.7-100% respectively. The analytical sensitivity of the bio-chip was ~ 250 genome copies per assay.
CONCLUSION: The biochip has high sensitivity and specificity and could be useful for clinical microbiology studies and epidemiological surveillance of drug resistant (DR) M. tuberculosis. It is a highly accurate tool for screening for SLDR, significantly reducing the time for phenotypic drug susceptibility test (DST) results from weeks to a single day.



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**28. Patient mobility and travel distance to receive drug-resistant tuberculosis treatment, and their associations with loss to follow-up in Guizhou Province, China.**

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BACKGROUND: Drug-resistant tuberculosis (DR-TB) remains a public health crisis, with loss to follow-up (LTFU) being a crucial factor influencing its management. To inform effective TB control strategies, this study aimed to assess patient mobility, travel distances, and their associations with LTFU among DR-TB patients in Guizhou Province, China.
METHODS: Data were collected from a national tuberculosis surveillance system from 2019 to 2021. Patients were classified as non-movers (treated at a hospital within the same prefecture) or movers (treated at a hospital in a different prefecture). Two travel distances were measured using AutoNavi: Distance 1 (home to treatment hospital) and Distance 2 (home to local hospital). The difference between these distances was categorized as follows: (1) Equal distance, (2) Long-distance travel (Distance 1 > Distance 2), and (3) Short-distance travel (Distance 1 < Distance 2). Three logistic regression models assessed associations between exposures (movers vs. non-movers in Model 1, long vs. short Distance 1 in Model 2, long-distance travel vs. equal distance in Model 3) and LTFU.
RESULTS: Guizhou Province has nine prefectures, each with a designated DR-TB hospital. Of the 936 patients studied, 703 (75.1%) were from seven less developed prefectures, and 427 (60.7%) sought treatment in two developed prefectures. The two hospitals provided care for 660 (70.5%) patients (Guiyang:

547 patients, 58.4%; Zunyi: 113 patients, 12.1%). Among movers, 72.2% lived more than 100 km away. Overall, 28.5% of patients were LTFU. Adjusted analysis showed that movers had a higher LTFU risk [aOR = 1.49; 95% CI (1.04, 2.13) in Model 1], especially those with over 145 km Distance 1 [aOR = 1.74; 95% CI (1.11, 2.75) in Model 2] and long-distance travel [aOR = 1.45; 95% CI (1.01, 2.10) in Model 3]. CONCLUSION: DR-TB patients often travel from less developed prefectures to two major cities in Guizhou for better care. Patient mobility and travel burdens increase the risk of LTFU. Our study emphasizes the need to strengthen hospital infrastructure, improve DR-TB diagnosis and treatment in underdeveloped areas, and establish effective medication management and follow-up systems across all designated hospitals in the province to reduce DR-TB transmission and LTFU rates.



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**29. Rapid, accurate, and reproducible de novo prediction of resistance to Antituberculars.**

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As one of the deadliest infectious diseases in the world, tuberculosis is responsible for millions of new cases and deaths reported annually. The rise of drug-resistant tuberculosis, particularly resistance to first-line treatments like rifampicin, presents a critical challenge for global health, which complicates the treatment strategies and calls for effective diagnostic and predictive tools. In this study, we apply an ensemble-based molecular dynamics computer simulation method, TIES_PM, to estimate the binding affinity through free energy calculations and predict rifampicin resistance in RNA polymerase. By analyzing 61 mutations, including those in the rifampicin resistance-determining region, TIES_PM produces reliable results in good agreement with clinical reference and identifies abnormal data points indicating alternative mechanisms of resistance. In the future, TIES_PM is capable of identifying and selecting leads with a lower risk of resistance evolution and, for smaller proteins, it may systematically predict antibiotic resistance by analyzing all possible codon permutations. Moreover, its flexibility allows for extending predictions to other first-line drugs and drug-resistant diseases. TIES_PM provides a rapid, accurate, low-cost, and scalable supplement to current diagnostic pipelines, particularly for drug resistance screening in both research and clinical domains.IMPORTANCEAntimicrobial resistance (AMR), a global threat, challenges early diagnosis and treatment of tuberculosis (TB). This study employs TIES_PM, a free-energy calculation method, to efficiently predict AMR by quantifying how mutations in bacterial RNA polymerase (RNAP) affect rifampicin (RIF) binding. On simulating 61 clinically observed mutations, the results align with WHO classifications and reveal ambiguous cases, suggesting alternative resistance mechanisms. Each mutation requires ~5 h, offering rapid, cost-effective predictions. An ensemble approach ensures statistical robustness. TIES_PM can be extended to smaller proteins for systematic codon permutation analysis, enabling comprehensive antibiotic resistance prediction, or adapted to identify low-resistance-risk drug leads. It also applies to other TB drugs and resistant pathogens, supporting personalized therapy and global AMR surveillance. This work provides novel tools to refine resistance mutation databases and phenotypic classification standards, enhancing early diagnosis while advancing translational research and infectious disease control.

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**30. Impact of HIV and hospitalization on the incidence of subsequent rifampicin-resistant tuberculosis after initiation of first-line tuberculosis treatment: a retrospective cohort study in South Africa.**

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BACKGROUND: People living with human immunodeficiency virus (PLHIV) may have a higher risk of acquired rifampicin-resistance during first-line tuberculosis (TB) treatment, potentially driving the multi-drug or rifampicin-resistant tuberculosis (MDR/RR-TB) epidemic. Nosocomial transmission may further elevate MDR/RR-TB risk. We assessed the impact of HIV and hospitalization on subsequent MDR/RR-TB diagnosis among individuals starting first-line TB treatment.
METHODS: The retrospective cohort included individuals with laboratory-confirmed rifampicin-susceptible TB (RS-TB), who started TB treatment (2013-2021). Subsequent TB diagnoses (MDR/RR-TB and RS-TB) over 2 years' follow-up from TB treatment initiation were assessed. Routine health service data utilized.
FINDINGS: A total of 190,945 individuals were included; median age 34.0 (interquartile range (IQR), 25.5-44.9); 79,160 (42%) female and 69,636 (37%) PLHIV. Overall, 6870 (9.9%) PLHIV and 9342 (7.7%) HIV-negative individuals were diagnosed with recurrent TB within 24 months. Rifampicin drug susceptibility testing was available for 5354 (77.9%) and 8154 (87.3%) PLHIV and HIV-negative individuals, respectively. PLHIV with advanced HIV (cluster of differentiation 4

(CD4) <200 cells/μl) (adjusted-hazard ratio (HR) 2.86, 95% confidence interval (CI), 2.60-3.15) and individuals hospitalized (adjusted-HR 2.76, 95% CI, 2.50-3.05) for ≥1 week had significantly increased MDR/RR-TB risk compared to HIV-negative and non-hospitalized individuals, respectively. PLHIV had a higher risk of MDR/RR-TB relative to all other recurrent TB, regardless of CD4.
INTERPRETATION: This study suggests that PLHIV may have an increased risk of both acquiring rifampicin-resistance during TB treatment and re- or super-infection with already resistant Mycobacterium tuberculosis strain during hospitalization. While not causal, these data suggest the need for improved TB treatment for PLHIV including tailored drug regimens, potentially with increased rifampicin dosages, and emphasize the importance of TB infection control in healthcare settings.
FUNDING: The study received no funding.



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PMID: 41245538

Conflict of interest statement: All authors declare no competing interests.

**31. Off-label evaluation of the BD MAX MDR-TB assay for rapid diagnosis of rifampicin and isoniazid resistance of Mycobacterium tuberculosis clinical isolates in a high-volume reference laboratory.**

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Drug-resistant tuberculosis (TB) remains a primary global health concern. Multidrug-resistant TB is defined by resistance to at least rifampicin (RIF) and isoniazid (INH), the two key drugs used in TB treatment. The BD MAX Multi-Drug Resistant Tuberculosis (BD MAX) assay is a fully automated real-time PCR platform recommended by the World Health Organization for the initial diagnosis

of TB and RIF and INH resistance (RIF-R and INH-R) directly from pulmonary clinical samples. This study aimed to assess the off-label performance of BD MAX in clinical M. tuberculosis complex (MTBC) isolates under routine laboratory conditions. The assay was first validated using non-tuberculous mycobacteria (NTM) and MTBC isolates with known mutations. For real-world validation, it was compared to the GenoType MTBDRplus by testing 1,440 clinical isolates prospectively. The BD MAX assay correctly excluded MTBC from all NTM cultures. Among MTBC isolates with known mutations, it identified 19 of 20 RIF-R isolates and 14 of 15 INH-R isolates. In prospective testing, BD MAX achieved 99.6% sensitivity (1,403/1,409), 96.8% specificity (30/31), and 99.5% overall accuracy (1,433/1,440) for MTBC detection. For drug resistance detection, it showed 95.2% (40/42) concordance for RIF, 96.8% (30/31) for INH, and 81.3% (13/16) for MDR when compared to MTBDRplus. Discrepancies between MTBDRplus and BD MAX included heteroresistant cases and unreportable resistance results by BD MAX due to infrequent mutations or low bacterial load. Overall, this study confirms BD MAX as an accurate and reliable tool for MTBC detection and drug resistance profiling in clinical isolates in high-volume TB laboratories.IMPORTANCEThis study highlights the importance of the BD MAX Multi-Drug Resistant Tuberculosis assay (BD MAX) applied in clinical isolates for the detection of multidrug-resistant tuberculosis (MDR-TB), i.e., Mycobacterium tuberculosis resistance to rifampicin and isoniazid. TB is a global health issue, and drug-resistant TB makes treatment more difficult, favoring transmission and disease amplification. The BD MAX platform offers a faster and more automated way to detect TB and drug resistance. The study showed that BD MAX, applied off-label in clinical isolates, accurately identified TB and resistance to rifampicin and isoniazid, with results comparable to those of the widely used line probe assay. This is significant in a high-volume laboratory because it is more straightforward and more rapid than the line probe assay. BD MAX showed some limitations, especially in detecting rare mutations and in cases of low bacterial levels. Overall, this tool could improve TB care, especially in high-volume laboratories.

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Conflict of interest statement: The authors declare no conflict of interest.

**32. Latent Profile Analysis and Influencing Factors of Medication-Related Burden in Multidrug-Resistant Tuberculosis Patients in Chengdu, China.**

Patient Prefer Adherence. 2025 Nov 4;19:3387-3397. doi: 10.2147/PPA.S558068. eCollection 2025.

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OBJECTIVE: The treatment of multidrug-resistant tuberculosis (MDR-TB) is characterized by a prolonged duration and complex medication regimens, often resulting in a substantial medication-related burden that negatively impacts patients' adherence and quality of life. However, research on the heterogeneity of medication-related burden among MDR-TB patients and its influencing factors remains limited. This study aimed to identify latent profiles of medication-related burden among MDR-TB patients and examine differences in burden characteristics across these profiles, thereby providing evidence for tailored intervention strategies.
METHODS: A convenience sampling method was employed to recruit MDR-TB patients diagnosed at a tertiary infectious disease hospital in Chengdu between December 2024 and May 2025. Data were collected using a general information questionnaire, the Living with Medicines Questionnaire (LMQ), and the Health Literacy Management Scale (HeLMS). Latent profile analysis (LPA) was conducted to identify distinct profiles of medication-related burden, and multivariate logistic regression was used to explore associated factors for each profile.
RESULTS: A total of 214 valid responses were analyzed. The LPA identified two distinct profiles of medication-related burden: C1 - "Low-Burden (Attitude & Practice-Dominated)" (44%) and C2 - "High-Burden (Daily Interference-Dominated)" (56%). Absence of side effects, not employing a caregiver, and higher levels of health literacy were positively associated with membership in the C1 group ($P < 0.05$). In contrast, higher educational attainment, longer distance from the treatment center, and prolonged medication duration were negatively associated,

increasing the likelihood of being classified in the C2 group ($P < 0.05$).
CONCLUSION: Medication-related burden among MDR-TB patients exhibits clear heterogeneity. Healthcare professionals should adopt stratified management and personalized interventions based on the identified influencing factors to alleviate the burden of medication in this population.



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PMID: 41211182

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This study was supported by the Health Commission of Sichuan Province Medical Science and Technology Program. The funder had no role in the study design, data collection, analysis, interpretation, or decision to publish.

**33. Understanding predictors of medication adherence and treatment outcomes among TB patients in the Western Region, Ghana: strategies for strengthening TB control Efforts.**

J Health Popul Nutr. 2025 Nov 21;44(1):407. doi: 10.1186/s41043-025-01145-1.

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BACKGROUND: Tuberculosis (TB) remains a major public health challenge in low- and middle-income countries, including Ghana. In the Effia-Kwesimintsim Municipality of the Western Region, high treatment default rates raise concerns about multidrug-resistant TB. Since medication adherence is key to successful

treatment, this study examined the predictors of TB treatment adherence and their associations with treatment outcomes.
METHODS: A cross-sectional study was conducted among 139 adult TB patients identified from the district TB register. Data were collected using structured questionnaires at participants' households. Data was analyzed using STATA version 17. Descriptive statistics were used to present results in tables and charts. Chi-square tests and multivariable logistic regression were employed to assess associations between socio-demographic, community, and health system variables and TB medication adherence and treatment outcomes. Variables with $p < 0.05$ were considered statistically significant.
RESULTS: The overall adherence rate was 84.2%, while treatment success stood at 55%. Key predictors of adherence included employment status (aOR = 25.75, 95% CI: 1.71-87.59), presence of a treatment supporter (aOR = 14.21, 95% CI: 2.23-19.70), and receiving a support package from a health facility (aOR = 13.83, 95% CI: 1.11-17.02). Adherence was strongly associated with treatment success (aOR = 5.22, 95% CI: 1.22, 12.48), and employed individuals had increased odds of successful treatment (aOR = 3.1, 95% CI: 1.28-7.57). Fear of stigma, economic barriers, and lack of social support were reported as primary reasons for non-adherence.
CONCLUSION: Medication adherence is strongly associated with TB treatment success, surpassing individual factors like age and gender. The findings highlight the importance of strengthening adherence through social support systems, economic assistance, community-based interventions, and employment-related policies. Enhancing access to care through CHPS initiatives, aligning TB care with Ghana's universal health coverage and social protection frameworks, may support better health outcomes and contribute to achieving national and global TB control targets.



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PMID: 41272782 [Indexed for MEDLINE]

Conflict of interest statement: Declarations. Ethical consideration: Permission was sought from the University of Health and Allied Sciences Research Ethics Committee (UHAS-REC) with a protocol identification number UHAS-REC B.10[012] 21–22 was obtained. Appropriate permission was sought from the Effia Kwesimintsim Municipal Health Directorate before the study commenced. The study adhered to the ethical principles outlined in the Declaration of Helsinki. All participants were recruited into the study after giving full consent. Participants were assured of absolute confidentiality and had the right to refuse participation without consequences. All personal identification was excluded from the data. Consent for publication: Not applicable. Competing

interests: The authors declare no competing interests.

**34. Time to sputum culture conversion and associated factors in multidrug-resistant tuberculosis patients in Southwestern Oromia, Ethiopia: a ten-year retrospective follow-up study.**

BMC Pulm Med. 2025 Nov 11;25(1):518. doi: 10.1186/s12890-025-03986-2.

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BACKGROUND: Sputum culture conversion is an important predictor of treatment response and patient outcome in pulmonary multidrug-resistant or rifampicin-resistant tuberculosis (MDR/RR-TB). However, the determinants of time to culture conversion and its association with treatment regimens among MDR/RR-TB patients in Southwestern Oromia remain poorly understood. This study aimed to determine the time to initial sputum culture conversion and associated factors among pulmonary MDR/RR-TB patients in Southwestern Oromia, Ethiopia.
METHODS: We conducted a retrospective follow-up study on 168 MDR/RR-TB patients who had initiated treatment and followed up between 2013 and 2023 at centers in the Southwestern Oromia region of Ethiopia. A semi-structured data collection tool was used to extract demographic, clinical and bacteriological data. The median time to sputum culture conversion was analysed using Kaplan–Meier survival curves. Bivariate and multivariate Cox proportional hazards regression analyses were employed to identify factors associated with delayed time to sputum culture conversion. A p-value less than 0.05 was considered statistically significant.
RESULTS: Of the 168 participants, 85.7% (144) achieved culture conversion during a total follow-up of 397.8 person-months. Among those converted, 48.6% (70/144) achieved conversion within two months, 42.4% (61/144) within three to four months, and 9% (13/144) after four months of treatment. The median time to sputum culture conversion was 62 days (IQR: 32-92). The median time to culture conversion was longer for smear-positive samples (63 days, IQR: 32-93 days) than for smear-negative samples (59 days, IQR: 30-90 days, chi2 = 6.68, P

value = 0.0098). Patients receiving a shorter MDR/RR-TB regimen were twice as likely to achieve culture conversion faster than those receiving longer regimens (aHR = 1.85, 95% CI: 1.11-3.08, P = 0.019).
CONCLUSION: The median time to initial sputum culture conversion was 62 days, which was lower than the 4-month threshold considered a potential indicator of treatment failure according to the World Health Organization. MDR/RR-TB patients with HIV coinfection, higher baseline smear grades and those on longer treatment regimens were shown to have a delayed time to culture conversion. Attention should be given to these patients during their MDR/RR-TB treatment course to reduce delays in culture conversion and improve treatment outcomes.



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PMID: 41219969 [Indexed for MEDLINE]

Conflict of interest statement: Declarations. Ethics approval and consent to participate: This study was conducted following the principles stated in the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board (IRB) of the Institute of Health of Jimma University, Ethiopia (Reference: IHRPGn/168/21). Moreover, official permission was also obtained from all study sites. Since the study was retrospective and did not involve any personally identifiable information, the ethical committee waived the requirement for informed consent. To protect the privacy and confidentiality of the participants, patient names and identification numbers were not extracted. Consent for publication: Not applicable. Competing interests: The authors declare no competing interests.

**35. Genomic characterization and epidemiology of Mycobacterium tuberculosis lineage 2 isolates from Kazakhstan.**

Sci Rep. 2025 Oct 28;15(1):37715. doi: 10.1038/s41598-025-22485-2.

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Kazakhstan has one of the highest incidence rates of MDR-TB in the WHO European Region. However, data on the genomic diversity of circulating Mycobacterium tuberculosis strains in Kazakhstan remains limited. We performed whole-genome sequencing on 177 clinical M. tuberculosis isolates belonging to the L2/Beijing lineage, sourced from 15 regions across Kazakhstan. WGS data were analyzed using the computational genomics pipelines TB-Profiler, TB-Annotator, and MTBseq. We then carried out Bayesian analyses using the BEAST algorithm to predict the effective population size dynamics of M. tuberculosis in Kazakhstan over the last 50 years. Phenotypic drug susceptibility testing revealed a significant proportion of MDR (46.9%) and pre-XDR (14.7%) isolates. Phylogenetic analysis showed that 67.2% of M. tuberculosis L2/Beijing isolates belonged to the Central Asian outbreak (CAO) sublineage. Putative compensatory variants were detected in 89.6% of RIF-resistant CAO isolates, with rpoABC variants showing strong sublineage specificity. Furthermore, phylogenetic analysis contributed to the identification of six novel historical clusters, each characterized by distinct SNP signatures. Phylogenetic reconstruction indicated recent transmission and clonal expansion of CAO isolates. Meanwhile, Bayesian skyline analysis revealed a marked increase in the effective population size of Mtb. This study used genomic characterization to show that the CAO sublineage of M. tuberculosis lineage 2 has been highly successful during the MDR-TB epidemic in Kazakhstan, which has coincided with major economic fluctuations.

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PMID: 41152417 [Indexed for MEDLINE]

Conflict of interest statement: Declarations. Competing interests: The authors declare no competing interests.

**36.Tuberculosis laboratory capacity building in the WHO African Region: The past, the present and the future: A Viewpoint.**

PLOS Glob Public Health. 2025 Nov 11;5(11):e0004979. doi: 10.1371/journal.pgph.0004979. eCollection 2025.

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Tuberculosis remains a leading infectious disease killer in the World Health Organization African Region, with 2.5 million cases and 404,000 deaths in 2023, including 112,000 people with HIV. There is slow progress with only 42% of the 75% targeted reduction in death by 2025. Out of 60,266 estimated multidrug-resistant TB cases in 2023, only 22,515 were notified. Laboratory diagnostic services in the African region still need urgent attention. By 2005, the new smear-positive case detection rate was nearly 51%, falling short of the 70% target. By 2015, the benchmark for one microscopy center per 100,000 population was reached in some Member States, but gaps remained in culture and drug susceptibility testing coverage. Molecular tests were adopted, however there is slow uptake among countries to use them as initial diagnostic tests. The Global Laboratory Initiatives were established in 2007 and 2013 globally and

in the WHO African Region respectively to enhance access to quality-assured TB laboratory services. The WHO TB Supranational Reference Laboratory (SRL) Network was established in 1994 and expanded to the African region, including South Africa, Uganda, and Benin. The nomination of Mozambique and Rwanda in 2021 as candidate SRLs aims to strengthen this network. Future perspectives involve leveraging the established TB laboratory networks to integrate systems for diagnosing multiple diseases while enhancing efficiency. Advocacy for increased funding is vital for sustaining gains in the laboratory capacities, advancing universal health coverage and enhancing health outcomes in the African region. Here we discuss the TB laboratory capacity building in the WHO African region, focusing on the past, present and the future perspectives. We suggest recommendation towards sustaining and strengthening the existing achievements, while accelerating the laboratory interventions towards the End TB Strategy.



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Conflict of interest statement: Jean de Dieu IRAGENA, the author, is employed by WHO. However, the content of this paper represents personal views and not those of the employer.

**37. Cross-sectional analysis of tuberculosis burden and risk factors in Swabi district, Khyber Pakhtunkhwa, Pakistan.**

Trop Dis Travel Med Vaccines. 2025 Oct 22;11(1):37. doi: 10.1186/s40794-025-00270-3.

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Tuberculosis (TB) remains a serious public health concern in Pakistan, where it is considered endemic. Understanding the disease burden and its associated risk factors, particularly in an understudied population, is crucial for effective disease control. In this cross-sectional, hospital-based study, TB-suspected patients who visited the TB control centre of Swabi district, Khyber Pakhtunkhwa, Pakistan, during January 2023 to June 2024 were included. The aims and objectives of the study were to assess the frequency of TB and identify its associated risk factors and zoonotic TB within a population with limited access to healthcare services. After ethical approval, sociodemographic and clinical data were collected from individuals suspected of having TB, and statistical analyses were performed using the Chi-square test. A total of 1,164 individuals with suspected TB were included in our study. After microscopic and culture analysis, 232 were confirmed positive, comprising 118 males and 114 females. Of these, 218 individuals were infected by Mycobacterium tuberculosis, and 14 were infected by M. bovis. Furthermore, 10 cases were identified as multidrug-resistant tuberculosis (MDR-TB), 13 were reinfections, and 12 were extrapulmonary tuberculosis (EPTB) cases. The TB incidence was comparable across genders and different age groups; it was higher among people with comorbidities, low socioeconomic status, raising animals, and a smoking history. Notably, the detection of M. bovis in human cases and the association between animal presence and TB highlight the importance of incorporating the One Health approach strategies into TB control programs for effective control.
SUPPLEMENTARY INFORMATION: The online version contains supplementary material available at 10.1186/s40794-025-00270-3.

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PMCID: PMC12542393
PMID: 41126382

Conflict of interest statement: Declarations. Ethics approval and consent to participate: This study was conducted in accordance with the principles outlined in the Declaration of Helsinki, adhering to the ethical standards for medical research. Informed consent was obtained from all adult participants. For adolescents below the age of 18, permission was secured from their parents or legal guardians. All the patients were informed about the study objectives and aims. The research was approved by the Ethical Committee of the District TB Control Center, Swabi, Pakistan (F.1–7/NTB-S-KP/2023/05). The studies were conducted in agreement with the local legislation and institutional

requirements. Consent for publication: Not applicable. Competing interests: MSH declares that he also serves as an associate editor for Tropical Disease, Travel Medicine and Vaccines. However, the manuscript has undergone a fully independent and objective peer-review process, and the editorial decision was made without any influence from the author's role as an associate editor. All other authors declared no conflict of interest

**38. Analysis of Adverse Drug Reactions of Clofazimine Reported in the FDA Adverse Event Reporting System from 2004 to 2025 Q1.**

Infect Dis Ther. 2025 Nov;14(11):2489-2507. doi: 10.1007/s40121-025-01224-0. Epub 2025 Sep 13.

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INTRODUCTION: Clofazimine (CFZ) is an antimycobacterial agent used primarily for leprosy and multidrug-resistant tuberculosis. Despite its long clinical history, comprehensive pharmacovigilance data remain limited. This study aimed to analyze CFZ-associated adverse events (AEs) reported in the FDA Adverse Event Reporting System (FAERS), identifying and pharmacovigilance signals.
METHODS: We conducted a retrospective pharmacovigilance analysis of the FAERS database from 2004 to 2025 Q1. ASCII-format data were imported into R 4.4.2 and deduplicated using FDA guidelines. Reports Listing CFZ as the primary suspect drug were identified using generic and brand names. AEs were coded using MedDRA 27.1. Disproportionality analyses, including reporting odds ratio (ROR), proportional reporting ratio (PRR), Bayesian confidence propagation neural

network (BCPNN), and empirical Bayesian geometric mean (EBGM), identified signals of disproportionate reporting. Subgroup analyses examined sex differences, while time-to-onset (TTO) analyses characterized latency patterns. RESULTS: A total of 1287 CFZ-related AE reports were identified, with 995 (77.3%) classified as serious. Death (11.6%) and hospitalization (18.1%) were the most frequent serious outcomes. The majority of reports originated from the United States (59.4%). Demographic analysis showed higher reporting among females (49.6%) and patients aged 18-64 years (46.5%). Disproportionality analyses identified 135 preferred terms with positive safety signals. The most prominent signals included QT prolongation (ROR ~ 37.61), drug resistance (ROR ~ 17.31), skin hyperpigmentation (ROR ~ 13.07), and respiratory failure (ROR ~ 7.46), ranging from moderate to strong signal intensity. Subgroup analyses revealed significant sex differences in specific AE signals. TTO analysis indicated varied latency distributions across System Organ Class (SOC) and preferred term levels.
CONCLUSION: Our pharmacovigilance assessment of FAERS data from 2004 to 2025 not only identified multiple serious and consistent safety signals associated with clofazimine such as prolonged QT intervals but also revealed a life-threatening AE respiratory failure. Although the analysis of these AEs cannot directly reflect causal relationships due to the nature of the FAERS data from spontaneous reporting, our findings highlight the critical importance of continuous pharmacovigilance, targeted clinical monitoring, and consideration of sex-based risk differences to ensure the safe use of clofazimine in clinical practice.



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Conflict of interest statement: Declarations. Conflict of Interest: All authors (Ruoyu Zhang, Yunwen Tao, Ziwei Bao, Jianping Zhang, Lingwu Zeng, Chen Fang, Meiying Wu) declare no conflict of interest. Ethical Approval: The data used in this study were obtained from the publicly available FDA Adverse Event Reporting System (FAERS) database, which contains de-identified data. Therefore, the data is non-identifiable, and no personal identifying information was included in the dataset. As the data is non-identifiable, there was no need for additional ethical review for individual consent.

**39. Xpert MTB/RIF Ultra assay for tuberculosis disease and rifampicin resistance in Children.**

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Update of
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BACKGROUND: In 2023, an estimated 1.3 million children (aged 0-14 years) became ill with tuberculosis, and 166,000 children (aged 0-15 years) died from the disease. Xpert MTB/RIF Ultra (Xpert Ultra) is a molecular World Health Organization (WHO)-recommended rapid diagnostic test that detects Mycobacterium tuberculosis complex and rifampicin resistance. This is an update of a Cochrane review first published in 2020 and last updated in 2022. Parts of the current update informed the 2024 WHO updated guidance for the diagnosis of tuberculosis.
OBJECTIVES: To assess the diagnostic accuracy of Xpert Ultra for detecting pulmonary tuberculosis, tuberculous meningitis, lymph node tuberculosis, and rifampicin resistance in children (aged 0-9 years) with presumed tuberculosis.
SEARCH METHODS: We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, three other databases, and three trial registers

without language restrictions to 6 October 2023.
SELECTION CRITERIA: For study design, we included cross-sectional and cohort studies and randomized trials that evaluated Xpert Ultra in HIV-positive and HIV-negative children aged birth to nine years. Regarding specimen type, we included studies evaluating sputum, gastric, stool, or nasopharyngeal specimens (pulmonary tuberculosis); cerebrospinal fluid (tuberculous meningitis); and fine needle aspirate or surgical biopsy tissue (lymph node tuberculosis). Reference standards for detection of tuberculosis were microbiological reference standard (MRS; including culture) or composite reference standard (CRS); for stool, we considered Xpert Ultra in sputum or gastric aspirates in addition to culture. Reference standards for detection of rifampicin resistance in sputum were phenotypic drug susceptibility testing or targeted or whole genome sequencing.
DATA COLLECTION AND ANALYSIS: Two review authors independently extracted data and assessed methodological quality using the tailored QUADAS-2 tool, judging risk of bias separately for each target condition and sample type. We conducted separate meta-analyses for detection of pulmonary tuberculosis, tuberculous meningitis, lymph node tuberculosis, and rifampicin resistance. We used a bivariate model to estimate summary sensitivity and specificity with 95% confidence intervals (CIs). We assessed certainty of evidence using the GRADE approach.
MAIN RESULTS: This update included 23 studies (including 9 new studies since the previous review) that evaluated detection of pulmonary tuberculosis (21 studies, 9223 children), tuberculous meningitis (3 studies, 215 children), lymph node tuberculosis (2 studies, 58 children), and rifampicin resistance (3 studies, 130 children). Seventeen studies (74%) took place in countries with a high tuberculosis burden. Overall, risk of bias and applicability concerns were low. Detection of pulmonary tuberculosis (microbiological reference standard) Sputum (11 studies) Xpert Ultra summary sensitivity was 75.3% (95% CI 68.9% to 80.8%; 345 children; moderate-certainty evidence), and specificity was 95.9% (95% CI 92.3% to 97.9%; 2645 children; high-certainty evidence). Gastric aspirate (12 studies) Xpert Ultra summary sensitivity was 69.6% (95% CI 60.3% to 77.6%; 167 children; moderate-certainty evidence), and specificity was 91.0% (95% CI 82.5% to 95.6%; 1792 children; moderate-certainty evidence). Stool (10 studies) Xpert Ultra summary sensitivity was 68.0% (95% CI 50.3% to 81.7%; 255 children; moderate-certainty evidence), and specificity was 98.2% (95% CI 96.3% to 99.1%; 2630 children; high-certainty evidence). Nasopharyngeal aspirate (6 studies) Xpert Ultra summary sensitivity was 46.2% (95% CI 34.9% to 57.9%; 94 children; moderate-certainty evidence), and specificity was 97.5% (95% CI 95.1% to 98.7%; 1259 children; high-certainty evidence). Xpert Ultra sensitivity was lower against CRS than against MRS for all specimen types, while the specificities were similar. Extrapulmonary tuberculosis Meta-analysis was not possible for lymph node tuberculosis and tuberculous meningitis due to low study numbers. Interpretation of results For a population of 1000 children, where 100 have pulmonary tuberculosis: In sputum: • 112 would be Xpert Ultra positive, of whom

75 would have pulmonary tuberculosis (true positives) and 37 would not (false positives). • 888 would be Xpert Ultra negative, of whom 863 would not have pulmonary tuberculosis (true negatives) and 25 would have pulmonary tuberculosis (false negatives). In gastric aspirate: • 151 would be Xpert Ultra positive, of whom 70 would have pulmonary tuberculosis (true positives) and 81 would not (false positives). • 849 would be Xpert Ultra negative, of whom 819 would not have pulmonary tuberculosis (true negatives) and 30 would have pulmonary tuberculosis (false negatives). In stool: • 85 would be Xpert Ultra positive, of whom 68 would have pulmonary tuberculosis (true positives) and 17 would not (false positives). • 915 would be Xpert Ultra negative, of whom 883 would not have pulmonary tuberculosis (true negatives) and 32 would have pulmonary tuberculosis (false negatives). In nasopharyngeal aspirate: • 68 would be Xpert Ultra positive, of whom 46 would have pulmonary tuberculosis (true positives) and 22 would not (false positives). • 932 would be Xpert Ultra negative, of whom 878 would not have pulmonary tuberculosis (true negatives), and 54 would have pulmonary tuberculosis (false negatives). Detection of rifampicin resistance
Three studies with 76 children evaluated detection of rifampicin resistance (sputum only); two of these studies reported no cases and one reported rifampicin resistance in two children.
AUTHORS' CONCLUSIONS: Xpert Ultra sensitivity was moderate in sputum, gastric aspirate, and stool specimens. Nasopharyngeal aspirate had the lowest sensitivity. Xpert Ultra specificity was high against both MRS and CRS. We were unable to determine the accuracy of Xpert Ultra for detecting tuberculous meningitis, lymph node tuberculosis, and rifampicin resistance due to a paucity of data.
FUNDING: This update was funded through WHO.
REGISTRATION: The protocol for this review was originally published through Cochrane in 2019. The protocol for this update was a generic protocol that consolidated previously published Cochrane protocols of Xpert Ultra for tuberculosis detection and can be accessed at https://osf.io/26wg7/. Protocol (2019) DOI: 10.1002/14651858.CD013359 Original review (2020) DOI: 10.1002/14651858.CD013359.pub2 Review update (2022) DOI: 10.1002/14651858.CD013359.pub3.



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conflicts of interest.PA has no known conflicts of interest.LRI has no known conflicts of interest.MKSN has no known conflicts of interest.LGF has no known conflicts of interest.ME is a Cochrane Infectious Disease Group Editor, and has no known conflicts of interest. ME was not involved in the editorial process for this review. NI is a WHO staff member in the Global Tuberculosis Programme, which commissioned the 2024 update for tuberculosis molecular diagnostics.AKo is a WHO staff member in the Global Tuberculosis Programme, which commissioned the 2024 update for tuberculosis molecular diagnostics.SEV is a Medical Officer at the World Health Organization Global Tuberculosis Programme, which commissioned this review update for the 2022 WHO consolidated guidelines on the management of tuberculosis in children and adolescents.AB works as a technical officer at the WHO Global Tuberculosis Programme, which commissioned this review update for the 2022 WHO consolidated guidelines on the management of tuberculosis in children and adolescents. KV is a WHO staff member in the Global Programme on Tuberculosis and Lung Health, which commissioned the 2022 review for the Guideline Development Group meeting on TB in children and adolescents and the 2024 update for the TB diagnostics Guideline Development Group meeting.TM is a WHO consultant in the Global Programme on Tuberculosis and Lung Health, which commissioned the 2022 review for the Guideline Development Group meeting on TB in children and adolescents and the 2024 update for the TB diagnostics Guideline Development Group meeting.AMM has conducted prior primary research on tuberculosis diagnostics and has no known conflicts of interest. She has undertaken work as an independent contractor for Janssen Global Services.KRS has received financial support for the preparation of systematic reviews and educational materials, consultancy fees from the Foundation for Innovative New Diagnostics (FIND) (for the preparation of systematic reviews), honoraria, and travel support to attend WHO guidelines meetings. KRS was previously a Cochrane Infectious Diseases Group and DTA Editor. KRS was not involved in the editorial process for this review.YT is a Cochrane Editorial Board Member and was previously a Cochrane Infectious Diseases Group Editor. She was not involved in the editorial process for this review. The authors alone are responsible for the views expressed in this article, which do not necessarily represent the views, decisions, or policies of the institutions with which they are affiliated.

**40.Timosaponin B- II Enhances Osteogenic Differentiation of Human Periodontal Ligament Stem Cells via PI3K/AKT/GSK3β Signaling Pathway.**

Stem Cell Rev Rep. 2025 Nov;21(8):2675-2692. doi: 10.1007/s12015-025-10962-0. Epub 2025 Aug 28.

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BACKGROUND: This investigation aims to elucidate the effects of Timosaponin B-II (TB-II) on the proliferation and osteogenic differentiation of human periodontal ligament stem cells (hPDLSCs) through both in vitro experiments and an in vivo orthodontic tooth movement model utilizing rats. The primary objective is to clarify the mechanisms by which TB-II influences the remodeling of periodontal tissue under biomechanical stress, thereby providing insights into its potential role in reducing relapses after orthodontic tooth movement.
METHODS: hPDLSCs were isolated and characterized via flow cytometry and multilineage differentiation assays (osteogenic and adipogenic induction). The impact of TB-II on the expression levels of osteogenic genes and proteins, including runt-related transcription factor-2 (RUNX-2), alkaline phosphatase (ALP), and collagen type 1 (COL-1), was evaluated through quantitative real-time PCR (qRT-PCR) and Western blotting. Alizarin Red Staining (ARS) was utilized to assess the formation of mineralized nodules. Additionally, the involvement of the phosphatidylinositol - 3 - kinase (PI3K)/ protein kinase B(AKT)/ glycogen synthase kinase - 3β(GSK3β) signaling pathway in TB-II-mediated osteogenesis was explored using pharmacological inhibitors (LY294002 for PI3K/AKT and CHIR-99021 for GSK3β). Western blot analysis identified key osteogenic markers (GSK3β, p-GSK3β, AKT, p-AKT) in treated cells. For in vivo validation, eighteen male Wistar rats were randomly divided into TB-II-treated and saline-control groups. Micro-computed tomography (micro-CT) evaluated tooth movement and alveolar bone structural changes. Histological assessment included hematoxylin-eosin (HE) staining, Masson trichrome staining, and tartaric-resistant acid phosphatase (TRAP) staining to analyze periodontal tissue morphology. Immunohistochemical (IHC) analysis assessed osteogenic markers (RUNX-2, ALP, COL-1) and the osteoclastogenic regulator RANKL to evaluate tissue remodeling. All statistical analyses were performed using GraphPad Prism 8. Comparisons between groups were conducted via one-way/two-way ANOVA with Tukey's post-hoc test. Values of $p < 0.05$ were regarded as statistically significant.
RESULTS: In vitro studies revealed that TB-II at 20 μM significantly enhanced

the proliferation, ALP activity, and mineralized nodule formation of hPDLSCs, accompanied by markedly elevated expression of RUNX-2, ALP, COL-1, p-AKT and p-GSK3β. Pharmacological inhibition of the PI3K/AKT pathway via LY294002 abolished TB-II's osteogenic effects, while treatment with CHIR99021 indicated that GSK3β activity was downstream and regulated by the PI3K/AKT signaling axis. In vivo, TB-II administration in a rat orthodontic tooth movement (OTM) model upregulated RUNX-2, ALP, and COL-1 expression on the tension side of tooth roots, while simultaneously reducing TRAP + osteoclast numbers and inhibiting RANKL expression.
CONCLUSION: TB-II stimulates the proliferation and osteogenic maturation of hPDLSCs in vitro by activation of the PI3K/AKT/GSK3β signaling axis. In vivo investigations using OTM model further demonstrate that TB-II enhances periodontal tissue regeneration. Collectively, these results highlight the therapeutic potential of TB-II in preventing relapses following OTM, positioning it as a viable candidate for clinical strategies aimed at stabilizing orthodontic outcomes.



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**41. TAK1 phosphorylation mediates macozinone (PBTZ169) induced innate immune activation against tuberculosis.**

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The management of tuberculosis (TB), particularly drug-resistant variants, presents enduring clinical challenges characterized by complex therapeutic regimens, prolonged treatment durations, suboptimal success rates, and significant adverse effects, issues that have persisted as critical concerns in global healthcare. Current TB drug development predominantly focuses on novel compounds and combination therapies targeting pathogen-specific pathways while overlooking the influence of different drugs on host immunity, which is indeed a key factor affecting treatment-related tissue damage and treatment time. In this study, we evaluated the effects of important anti-TB drugs and candidate drugs on host innate immunity and found that PBTZ169 showed potent innate immunity activator, which is a promising drug for the treatment of drug-sensitive and -resistant TB. The expression of cytokines and type I interferon was strongly upregulated by PBTZ169 under lipopolysaccharide (LPS) stimulation and PBTZ169-resistant strain infection, and the innate immune activation enhanced antibacterial activity in macrophages. Mechanistically, PBTZ169 upregulated the NF-kB and MAPK signaling pathways by activating the phosphorylation of TAK1. TAK1 knockdown abrogated PBTZ169-mediated immune activation and antibacterial effects. We thus demonstrate for the first time that PBTZ169 up-regulates NF-κB and MAPK innate immune signaling pathways via activating TAK1 phosphorylation, which may inform clinical deployment strategies and patient selection.IMPORTANCEMaintaining immune homeostasis is paramount for efficient Mycobacterium tuberculosis (Mtb) clearance and tissue repair. Current therapeutic strategies, however, predominantly focus on achieving maximal bacterial suppression within compressed timelines while overlooking the immunomodulatory consequences of anti-tuberculosis agents. This critical knowledge gap underscores the urgent need for mechanistic investigations to establish evidence-based frameworks for optimizing drug combinations and integrating therapies with host-directed approaches.

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**42. The role of cytochrome bc(1) inhibitors in future tuberculosis treatment Regimens.**

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Tuberculosis (TB) remains the foremost cause of death from infectious diseases globally, prompting ongoing efforts to improve treatment options. This includes developing compounds with novel modes of action and identifying optimal treatment regimens that allow for treatment shortening. One promising strategy involves targeting cytochrome bc1 oxidase in Mycobacterium tuberculosis, a key enzyme in the respiratory chain. In this study, we evaluate the potential of cytochrome bc1 inhibitors as partner drugs in TB combination regimens. Using a relapsing mouse model, we demonstrate that these inhibitors enhance regimen sterilisation and significantly reduce the time required for effective treatment. We also propose several novel combination strategies for both multidrug-resistant and drug-sensitive TB, where cytochrome bc1 inhibitors contribute to sterilisation and improved treatment outcomes. Furthermore, M. tuberculosis clinical isolates exhibited heightened susceptibility to cytochrome bc1 inhibitors compared to laboratory-adapted strains, highlighting the importance of using clinical isolates in TB drug discovery to better reflect the diversity of TB populations. These findings emphasise the potential of cytochrome bc1 inhibition in the development of more effective and shorter treatment regimens for TB, supporting the need for further clinical investigation.



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**43. Whole genome sequencing to characterize the molecular epidemiology and drug-resistance of tuberculosis in Huzhou, China.**

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BACKGROUND: Whole-genome sequencing (WGS) has emerged as a powerful tool for elucidating Mycobacterium tuberculosis (MTB) transmission dynamics and drug resistance patterns. In China, the application of WGS in TB surveillance has been rapidly expanding. However, molecular epidemiological studies based on WGS data from low-incidence areas remain limited. Huzhou City, located in northern Zhejiang Province, reported a TB incidence rate of 27.16 per 100,000 population in 2024, which was lower than both the national and provincial averages. In July 2023, Huzhou pioneered China's first "TB-Free City" initiative. To support public health efforts and facilitate the development of a WGS-based molecular surveillance network tailored for low-incidence settings, we performed WGS on 350 MTB isolates obtained from culture-positive TB patients in Huzhou between March 2023 and September 2024. Phylogenetic analysis, drug resistance profiling, and transmission cluster identification (using a ≤ 12 SNP threshold) were conducted to characterize the molecular epidemiology of TB in this region.
RESULTS: Lineage 2.2.1 (Beijing genotype) was predominant (80.0%). A total of 86 isolates (24.6%) harbored drug resistance-associated mutations, including 2.0% MDR-TB and 1.7% pre-XDR-TB, with no XDR-TB or resistance to bedaquiline, linezolid, or delamanid detected. We identified 28 genomic clusters comprising 65 isolates (18.6%), with a clustering rate of 11.6% among DR-TB cases. Furthermore, 79.1% (68/86) of drug-resistant TB (DR-TB) cases were likely attributable to recent transmission, with clustered DR-TB strains sharing identical resistance-conferring mutations. Comparative analysis revealed that patients under 60 years of age were significantly more likely to be involved in recent transmission events (P = 0.035), while lineage, gender, occupation, treatment history, and local residency were not statistically associated with clustering.
CONCLUSIONS: Our findings suggest that recent transmission, particularly among younger individuals, contributes substantially to the DR-TB burden in Huzhou. WGS-based surveillance revealed moderate resistance levels and limited transmission, supporting the ongoing "TB-Free City" initiative. Enhanced genomic monitoring and early intervention targeting younger, mobile populations may

further curb TB transmission in low-incidence settings.
SUPPLEMENTARY INFORMATION: The online version contains supplementary material available at 10.1186/s12864-025-12202-8.

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**44. A Prospective Cohort Study on the Usage, Safety, and Efficacy of Delamanid in Patients With Pulmonary Multidrug-Resistant Tuberculosis in South Korea.**

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BACKGROUND: Delamanid has demonstrated potential in the treatment of multidrug-resistant (MDR) or rifampicin-resistant tuberculosis (TB); however, real-world data on its effectiveness and safety remain limited.
METHODS: This prospective cohort study enrolled patients with pulmonary MDR-TB who were treated with a delamanid-containing longer regimen under programmatic conditions in South Korea between 2017 and 2021. Data on delamanid usage, safety, and efficacy were analyzed separately.
RESULTS: In total, 147 patients were included in the usage and safety analyses (mean age, 50.7 years; 60.5% male). Adherence to delamanid was high, with a median adherence of 100.0%; 98.6% (n = 145) of the patients received more than 80% of the prescribed dose. Delamanid-related adverse events (AEs) occurred in 44.2% (n = 65) of patients, with the most common AEs being nausea (10.9%), pruritus (6.8%), and QT interval prolongation (6.1%). Serious delamanid-related AEs were reported in 4.1% (n = 6) of the patients, and QTcF intervals exceeding 500 ms were observed in 6.8% (n = 10) during treatment. For the efficacy analysis, 105 and 122 patients were included in the treatment response (at the end of delamanid treatment) and treatment outcome (at the end of MDR-TB treatment) evaluations, respectively. Among those who were culture-positive at baseline, 92.0% achieved sputum culture conversion during delamanid treatment. The overall treatment success rate was 86.9%.
CONCLUSIONS: Delamanid demonstrated favorable safety and efficacy profiles for MDR-TB treatment under programmatic conditions, providing valuable and up-to-date evidence supporting its promising role in MDR-TB management.



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**45. Determinants of tuberculosis treatment adherence among patients taking anti-TB drugs in Borama, Somaliland.**

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BACKGROUND: Tuberculosis (TB) treatment non-adherence poses significant challenges, leading to complications, disease transmission, and drug resistance. This study aimed to identify the determinants of TB treatment adherence among adult patients attending the Borama Regional Hospital (BRH) in Somaliland.
METHODS: A cross-sectional study was conducted at BRH. Data were collected using a structured questionnaire, which included a direct question on missed doses (self-report), pill counts, and a validated 8-item Self-Administered Questionnaire to measure adherence. Statistical analysis included descriptive statistics, chi-square tests, independent t-tests, and binary and multivariable logistic regression using SPSS version 26 to identify adherence-related factors. Adherence was defined as taking at least 95% of prescribed medications in the last 30 days based on a composite measure of self-report, pill count, and the self-administered questionnaire.
RESULTS: Of the 167 participants, 74.9% demonstrated adherence to Tuberculosis (TB) treatment. Multivariable logistic regression revealed that being employed (Adjusted Odds Ratio [AOR]: 0.058, 95% CI: 0.014-0.451) and self-employed (AOR: 0.201, 95% CI: 0.050-0.981) were associated with lower odds of adherence compared to being non-employed. Conversely, correctly following overall medical advice (AOR: 2.023, 95% CI: 1.832, 4.729), experiencing stigma (AOR: 3.744, 95% CI: 1.610-7.485), and traveling a long distance to the health facility (AOR: 7.526, 95% CI: 3.472-9.419) were associated with higher odds of adherence. Good housing conditions had a protective effect against non-adherence (AOR: 0.071, 95% CI: 0.21-0.531).
CONCLUSION: This study identified several factors significantly associated with TB treatment adherence in Borama. To improve treatment adherence, interventions should focus on addressing stigma, promoting access to healthcare, addressing socioeconomic determinants including housing, and addressing the financial and logistical limitations experienced by TB patients. They should also focus on adherence to medical advice.



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PMID: 41194122 [Indexed for MEDLINE]

Conflict of interest statement: Declarations. Ethics approval and consent to participate: Before the survey, the participants were informed of the study goals and confidentiality and provided written informed consent. No human body samples were used in this investigation, and no personally identifiable information was gathered that could compromise anonymity. The highest ethical standards were employed throughout the study, which was conducted in accordance with the Declaration of Helsinki. The Borama Regional Hospital approved this study under registration number BRH 55/2024, and the Amoud University Research Ethics Committee provided approval with reference 0130-AU-REC-2024. Consent for publication: Not applicable. This manuscript does not contain any person's data in any form (including individual details, images, or videos) that would require consent for publication. Competing interests: The authors declare no competing interests.

**46. RapTB: a lung-derived hemoglobin fragment with activity against Mycobacterium Tuberculosis.**

Front Microbiol. 2025 Oct 24;16:1669022. doi: 10.3389/fmicb.2025.1669022. eCollection 2025.

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Tuberculosis (TB) remains difficult to treat due to the need for prolonged multidrug therapy and the global rise of drug-resistant Mycobacterium tuberculosis (Mtb) strains. Endogenous antimicrobial peptides (AMPs) have emerged as promising candidates for host-directed therapies. Given the pulmonary nature of TB, we hypothesized that human lung tissue contains peptides with

intrinsic antimycobacterial activity. We screened a peptide library derived from human lung tissue and identified a 39-amino-acid C-terminal fragment of β-hemoglobin (HBB(112-147)), referred to as RapTB, with potent activity against Mtb. Recombinant RapTB exhibited dose-dependent inhibition of extracellular Mtb, reaching ~60% activity at 50 μM. Electron microscopy revealed mycobacterial cell wall disruption as a likely mechanism. RapTB was non-toxic to primary human macrophages and efficiently internalized by Mtb-infected cells. However, it did not co-localize with intracellular bacilli and failed to limit intracellular replication. HBB-derived fragments such as RapTB have previously been identified in human tissues and are known to exhibit broad-spectrum antimicrobial activity. Our findings extend this functional class to include antimycobacterial activity and suggest a potential role for RapTB in the early, extracellular phase of host defense against TB.



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PMID: 41209728

Conflict of interest statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

**47. Post-treatment Lung Tuberculosis Sequelae: an Inexpensive Clinical-Laboratory Nomogram to Predict Tissue Destruction.**

Mediterr J Hematol Infect Dis. 2025 Nov 1;17(1):e2025075. doi: 10.4084/MJHID.2025.075. eCollection 2025.

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BACKGROUND: Post-treatment lung destruction (LD) impairs quality of life in pulmonary tuberculosis (TB) survivors, yet early risk-stratification tools are lacking. We aimed to develop and internally validate a clinical-laboratory nomogram to predict LD at completion of standard anti-TB therapy.
METHODS: In this retrospective cohort, we enrolled 205 treatment-naïve adults with pulmonary TB from April 2021 to April 2025. LD was defined on follow-up chest CT as extensive fibrosis, bronchiectasis with volume loss, or parenchymal destruction. Twenty-two baseline demographic, clinical, laboratory, and imaging variables were screened. Least absolute shrinkage and selection operator (LASSO; 10-fold cross-validation) was used for variable selection, followed by Akaike information criterion (AIC)-guided stepwise multivariable logistic regression. Model performance was compared with random forest (RF) and support vector machine (SVM) classifiers. Discrimination (area under the receiver-operating characteristic curve, AUC), calibration (bootstrap-corrected curve; Brier score), and clinical utility (decision-curve analysis, DCA) were assessed; internal validation used 1,000-sample bootstrap resampling.
RESULTS: LD occurred in 61/205 patients (29.8%). Nine predictors-silicosis, drug resistance, symptom-to-treatment delay, lymphocyte count, C-reactive protein, aspartate aminotransferase, γ-glutamyl transferase, albumin, and baseline atelectasis/cavity-composed the final model. The nomogram showed excellent discrimination (AUC = 0.93, 95% CI 0.897-0.971; optimism-corrected AUC = 0.93) and good calibration (Brier = 0.13). Across 10-40% risk thresholds, DCA indicated a higher net benefit than treat-all or treat-none strategies. Logistic regression slightly outperformed RF (AUC = 0.91) and SVM (AUC = 0.92) while retaining interpretability.
CONCLUSIONS: An inexpensive, easily applicable nomogram integrating routine clinical and laboratory indices accurately predicts post-treatment LD in TB patients. The tool can support personalized follow-up and timely interventions, warranting external validation in multicenter prospective cohorts.

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PMCID: PMC12611364
PMID: 41235028

Conflict of interest statement: Competing interests: The authors declare no competing interest.

**48.Extrapolation of lung pharmacokinetics of bedaquiline across species using physiologically-based pharmacokinetic modelling.**

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AIMS: Bedaquiline (BDQ) is a first-in-class diarylquinoline (DARQ) and a potent anti-tuberculosis drug, vital in combating multi-drug resistant tuberculosis (TB). Understanding its lung pharmacokinetics (PK) across species is crucial for effective clinical translation. This study aimed to extrapolate BDQ's lung PK from preclinical species to humans, focusing on healthy and TB-infected lung tissue.
METHODS: Physiologically-based PK (PBPK) modelling was employed to simulate BDQ's lung distribution in various pulmonary micro-compartments, including cellular lesions and caseous granulomas, using data from mice, rats and dogs. Complex interactions, such as lysosomal trapping within macrophages and anomalous diffusion within the caseum, utilising a catenary model and a time-dependent rate, were incorporated into the models to accurately represent BDQ's unique PK profile.
RESULTS: The study revealed intricate dynamics of BDQ's lung distribution, with only free concentrations in lysosomes of macrophages surpassing the MIC of Mycobacterium tuberculosis in both mice and humans, indicating intracellular accumulation which may further explain the proven drug's efficacy. Moreover, during the course of treatment in humans, adequate drug levels were achieved near the cellular rim but penetration into the inner caseous core was predicted to be limited.
CONCLUSIONS: Understanding BDQ's lung PK is essential for optimising dosing strategies with new companion drugs. The findings underscore the need to characterise BDQ distribution within the caseum, as it shows extensive caseum binding. Moreover, the developed PBPK model can be applied to new promising DARQ analogues, facilitating their development as effective TB treatments.



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Conflict of interest statement: The authors declare no conflict of interest.

**49. Comparing end-user diagnostic outputs from a commercial tNGS pipeline for Mycobacterium tuberculosis drug resistance detection.**

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eCollection 2025 Nov.

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BACKGROUND: Targeted next-generation sequencing has emerged as a rapid solution for diagnosing drug-resistant TB (DR-TB) directly from clinical specimens. Updating the bioinformatics software component can lead to rapid improvements in diagnostic performance. We compared the diagnostic performance of an updated bioinformatic pipeline output to the original pipeline output for the Oxford Nanopore Technology (ONT) TB Drug Resistance Test.
METHODS: A total of 721 sediment samples were evaluated for 13 anti-TB drugs using phenotypic drug susceptibility testing and whole genome sequencing. Sequencing data outputs previously analysed using the original pipeline were re-analysed using an updated pipeline and compared.
RESULTS: There were no significant differences in successful sequencing results, and direct comparison of DR-TB call agreement was substantial ($\kappa > 0.7$) between the original and updated pipeline outputs. Diagnostic accuracy relative to the composite reference standard was compared, and significant (P value < 0.05) increases in sensitivity and diagnostic yield, using the updated pipeline, were identified for streptomycin, pyrazinamide, bedaquiline, and clofazimine.

CONCLUSION: Comparison of the updated pipeline to the original pipeline revealed significant improvements in diagnostic performance, demonstrating that bioinformatic enhancements alone - without wet-lab modifications - can substantially boost sensitivity and diagnostic yield for DR-TB. These findings underscore the critical role of continuous pipeline optimisation in the evolving resistance landscape to enhance real-time clinical decision-making.



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**50. Prevalence of comorbidities and their impact on prognosis among patients with rifampicin-resistant tuberculosis: a multicenter retrospective cohort study in China.**

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Comorbidities are a significant factor affecting the prognosis of patients with rifampicin-resistant tuberculosis (RR-TB). We evaluated the prevalence of comorbidities and their prognostic effects in a Chinese RR-TB cohort. In this study, we reviewed the clinical data of RR-TB patients who started anti-tuberculosis treatment in China between May 2018 and April 2020 by conducting a multicenter cohort study. A log-binomial regression model was used to analyze the relationship between comorbidities and the treatment outcomes of RR-TB. The burden of comorbidities among RR-TB patients in China was heavy, with 49.45% (670/1355) experiencing at least one comorbidity. The most common comorbidities were diabetes (17.79%), followed by other respiratory diseases (11.14%), other liver and kidney diseases (5.31%), hypertension (5.24%), immunodeficiency (4.94%), viral hepatitis or carriers (3.91%), severe heart disease (2.58%), tumours (1.11%), and chronic kidney disease or renal insufficiency (0.74%). Diabetes (RR = 1.31), severe heart disease (RR = 1.70), tumours (RR = 1.89), hypertension (RR = 1.28), aged ≥ 60 years (RR = 1.64) and 45-59 years (RR = 1.38), ethnic minorities (RR = 1.58), retreatment cases (RR = 1.34), and those not using the bedaquiline regimen (RR = 1.92) significantly increased the risk of unfavorable treatment outcomes. While higher

education or above (RR = 0.49), employment (RR = 0.51), and having a normal (R = 0.53) or overweight (R = 0.56) BMI could reduce the risk of unfavorable treatment outcomes. Patients with RR-TB beared a substantial comorbidity burden in China. Notably, the presence of comorbidities such as diabetes, severe cardiac disorders, tumours, and hypertension markedly elevate the risk of adverse treatment outcomes in these patients. It is necessary to strengthen the screening and management of comorbidities to optimize the treatment strategies.



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PMID: 41193548 [Indexed for MEDLINE]

Conflict of interest statement: Declarations. Competing interests: The authors declare no competing interests. Ethical approval and informed consent: This study adhered to the tenets of the Declaration of Helsinki and was approved by the Ethics Committee of the Public Health Clinical Center of Chengdu as the lead center (Approval No. YJ-K2022-81-01). As a retrospective study using anonymized patient data, the requirement for informed consent was waived.

**51. Clinical and bacterial determinants of unfavorable tuberculosis treatment outcomes: an observational study in Georgia.**

Genome Med. 2025 Nov 14;17(1):143. doi: 10.1186/s13073-025-01555-0.

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BACKGROUND: Tuberculosis (TB) remains a major public health concern. Improving TB control programs and treatment success requires a deeper understanding of the factors that determine disease presentation and treatment outcomes. While the importance of patient factors is well established, our understanding of the bacterial determinants of disease presentation and treatment outcomes in TB remains limited.
METHODS: In this study, we analyzed the Mycobacterium tuberculosis complex (MTBC) genomes and the associated clinical data from 4529 TB patients in the country of Georgia covering a period of 13 years. We used multivariable modeling together with genome-wide association studies (GWAS) to identify patient and bacterial factors that determine TB disease manifestation and clinical outcomes.
RESULTS: Multivariable modelling confirmed the role of demographic and clinical factors in determining treatment outcomes, as well as the efficacy of novel TB treatments containing bedaquiline. In addition, we found that several bacterial factors, including the MTBC lineage, the specific mutations conferring resistance to rifampicin and fluoroquinolones, as well as a high bacterial burden, were associated with unfavorable outcomes. GWAS analyses revealed no bacterial genetic mutations associated with treatment outcomes beyond the known drug resistance-conferring mutations. However, we found that mutations in the bacterial gene sufD were linked to a reduced risk of lung cavities and a lower bacterial burden within patients. By contrast, specific mutations conferring resistance to rifampicin and fitness compensatory mutations were associated with a higher bacterial burden.
CONCLUSIONS: Our results show that both patient and bacterial factors determine disease presentation and clinical outcomes in TB. They also support the rationale of optimizing treatment regimens against drug-resistant TB with existing drugs based on the specific genetic features of the pathogen. Finally, our results highlight sufD as a possible therapeutic candidate.



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PMID: 41239519 [Indexed for MEDLINE]

Conflict of interest statement: Declarations. Ethics approval and consent to participate: The research was conducted in accordance with the Declaration of Helsinki. Competing interests: The authors declare no competing interests.

**52. Correlation between serum ANKRD22 and SERPING1 levels and drug resistance in pulmonary tuberculosis: A retrospective cross-sectional study.**

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10.1097/MD.0000000000045424.

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Drug-resistant tuberculosis (TB) lacks rapid blood-based biomarkers. This study examined whether serum levels of ankyrin repeat domain 22 (ANKRD22) and serpin family G member 1 (SERPING1) are associated with drug resistance in TB patients. In this retrospective cross-sectional study, 170 culture-confirmed TB patients treated from January 2023 to December 2023 were classified as drug-resistant (n = 34) or drug-susceptible (n = 136) by phenotypic drug susceptibility testing. We quantified serum ANKRD22 and SERPING1 levels by enzyme-linked immunosorbent assay, used multivariate logistic regression to identify independent risk factors, and assessed diagnostic performance with receiver operating characteristic curve analysis. Both biomarkers were significantly higher in the drug-resistant group (P < .001) and positively correlated with resistance (ANKRD22 R = 0.551, SERPING1 R = 0.520). Area under the curve values were 0.898 for ANKRD22, 0.875 for SERPING1, and 0.912 for combined detection. After adjustment, elevated ANKRD22 and SERPING1 remained independent predictors, along with smoking, chronic obstructive pulmonary disease, cavitary disease, previous TB exposure, and treatment interruption. Serum ANKRD22 and SERPING1 are independently associated with TB drug resistance; their combined measurement improves diagnostic accuracy and may facilitate early detection of drug-resistant TB.



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PMID: 41261705 [Indexed for MEDLINE]

Conflict of interest statement: The authors have no conflicts of interest to disclose.

**53. Rational Design and Antimycobacterial Evaluation of Aryl Sulfonamide-Linked Isoniazid Hydrazones Against Mycobacterium Tuberculosis.**

ChemMedChem. 2025 Nov 6;20(21):e202500398. doi: 10.1002/cmdc.202500398. Epub

2025 Sep 17.

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Despite significant advancements in antituberculosis (TB) drug discovery, considerable scope remains for novel therapeutic development. Molecular hybridization represents a promising strategy for generating new anti-TB agents. In this study, in silico molecular docking is employed to design novel isoniazid-sulfonamide hybrids connected via a hydrazone bridge, designated as series 7j-r and 8a-i. Docking analysis reveals that these compounds interact significantly with the active site of InhA, particularly engaging the catalytic triad residues Y158, F149, and K165, as well as the cofactor NAD. Subsequently, both series are synthesized and evaluated against Mycobacterium tuberculosis. Generally, compounds from both series (7 and 8) exhibit enhanced activity compared to their precursors. Notably, compound 8a demonstrated approximately twofold greater potency ( minimum inhibitory concentration (MIC) = 0.156 μg mL-1) with respect to compound 7j (MIC = 0.313 μg mL-1). However, these compounds lose efficacy against INH-resistant M. tuberculosis strains harboring katG mutations and remain ineffective against multidrug-resistant and extensively drug-resistant strains of M. tuberculosis. Encouragingly, the tested compounds exhibit little cytotoxicity against the THP-1 human monocytic cell line at a concentration of 20 μg mL-1. Additionally, the structural stability studies using 1H NMR confirm the structural integrity of these compounds. Overall, these molecular hybrids are promising for further development as anti-TB agents after relevant structural optimizations.



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PMID: 40962703 [Indexed for MEDLINE]

Conflict of interest statement: The authors declares no conflict of interest.

**54. Stigma and Time: A Longitudinal Qualitative Analysis of Co-occurring HIV and Tuberculosis Stigma in South Africa.**

AIDS Behav. 2025 Nov;29(11):3608-3616. doi: 10.1007/s10461-025-04803-x. Epub 2025 Jul 16.

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For people with HIV and tuberculosis (TB), stigma may change over time. Identifying time points when individuals are most likely to experience HIV or TB related stigma, or when stigma begins to abate, may be useful in tailoring stigma-reduction interventions in resource-limited settings. This study used longitudinal qualitative data to explore if and how HIV and TB stigma change over the course of treatment. People living with HIV and rifampicin-resistant TB were purposively recruited at a district TB hospital in KwaZulu-Natal, South Africa. Participants consented to in-depth interviews throughout TB treatment. The team used reflexive thematic analysis to develop latent themes within the transcripts. This study was designed to identify longitudinal changes stigma over time from the perspective of someone living with HIV and TB. However, participants were more expansive in their conceptualization of evolving stigma. 30 individuals discussed changes in stigma from three distinct perspectives. First was a perspective of lived experience, where participants described changes in experienced, internalized, and anticipated stigma over time beginning with diagnosis. The second was from a shifted perspective, as participants described their diagnosis and movement from status neutral to status positive transitioning from a potential enactor of stigma to someone at risk for experiencing stigma. Finally, participants described changes in stigma from the

community perspective whose attitudes towards HIV and TB disease were shaped by time. To strengthen care engagement, we must effectively intervene on disease-related stigma. Appropriate interventions must consider time and shifting social expectations that impact stigma.



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PMID: 40668459 [Indexed for MEDLINE]

Conflict of interest statement: Declarations. Conflict of Interest: The authors declare that they have no competing interests. Research Involving Human Participants: The Johns Hopkins University School of Medicine Institutional Review Board (approval # IRB00211518) and the University of Witwatersrand board of ethics (M190937) reviewed and approved this research protocol. This research was conducted in accordance with the Declaration of Helsinki. All study activities were conducted according to the approved protocol. Informed Consent: All participants provided written informed consent to participate in the parent study and the qualitative sub-study.

**55. Post-TB treatment completion experiences of children, adolescents, and caregivers from Cape Town.**

IJTLD Open. 2025 Nov 12;2(11):662-670. doi: 10.5588/ijtldopen.25.0117. eCollection 2025 Nov.

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BACKGROUND: Post-TB life is associated with a range of clinical, economic, social, and psychological sequelae, with limited data available on children and adolescents. We describe child TB survivors' physical, emotional, and social post-TB treatment experiences, in a high-incidence setting in South Africa.
METHODS: An explorative qualitative study was nested within the Umoya TB cohort between June and September 2023. We used semi-structured interviews and participatory methods, including body mapping, to explore participants' physical, emotional, and social wellbeing. Data were analysed using a deductive thematic approach and a health-related quality-of-life framework.
RESULTS: Thirty semi-structured interviews were conducted with 15 children/adolescents; median age 9 years (range: 5-15); 8 (53%) were male; 2 (13%) living with HIV, and 1 (6%) had multidrug-resistant TB. Most interviews were conducted with children together with their caregivers (N = 14). Interviews were done 11-61 months (41-month average) after TB treatment completion. All participants reported that TB significantly impacted their physical, psychological, and social domains, extending well beyond treatment completion. Children and adolescents perceived changes in their bodies like shortness of breath and physical pain following their TB episode, reporting various physical post-TB cure symptoms. TB-related stigma disrupted participants' social relationships, especially among adolescents. Broader underlying socio-environmental challenges exacerbated the long-term economic impact of TB on household financial instability.
CONCLUSION: The negative impacts of TB extend well beyond children and adolescents' treatment completion across multiple aspects of their lives. Future studies should prioritise the development of interventions to enhance communication and optimise follow-up care for paediatric TB survivors.



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PMCID: PMC12617085
PMID: 41246463

**56. Cost-effectiveness of modified fully oral 9-month treatment regimens for rifampicin-resistant tuberculosis in Belarus, Georgia, Kazakhstan and the Republic of Moldova.**

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INTRODUCTION: Prior to 2020, treatment options for multidrug-resistant tuberculosis (MDR-TB) were limited and typically involved long treatment durations and high financial burdens. In the eastern European and central Asian (EECA) region, traditional inpatient tuberculosis (TB) care models, alongside high MDR-TB rates, escalate nosocomial transmission risks and treatment costs. Modified, fully oral, shorter treatment regimens (mSTR) implemented in the WHO European Region under operational research conditions offered a potential reduction in the burden of MDR-TB treatment for both patients and health systems.
METHODS: We conducted the first regional evaluation of the cost-effectiveness of the novel mSTR treatment regimen compared with the standard of care (SOC) in Belarus, Georgia, Kazakhstan and Republic of Moldova. We used cohort data on mSTR efficacy and WHO data on SOC in patients with MDR-TB. We used a Markov model, with treatment costs calculated from the provider perspective. Outcomes were measured in quality-adjusted life years (QALYs), with incremental cost-effectiveness ratios (ICER) calculated per QALY gained in each country. An annual 3% discount rate was used for both costs and outcomes. We performed univariate and probabilistic sensitivity analysis (PSA) to assess the robustness of our cost-effectiveness calculations under varying assumptions. Finally, we estimated potential cost savings if mSTR was implemented nationally and we evaluated the incremental net monetary benefit (iNMB) and willingness-to-pay

(WTP) thresholds based on Wood et al's country-level cost-effectiveness thresholds. All costs were reported in 2022 USD.
RESULTS: We estimated that mSTR can reduce TB treatment costs by between 23% and 47% and drug costs by 39% to 74%, compared with SOC in the countries studied. mSTR resulted in cost savings of between $3596 and $8174 per patient and offered additional health gains of between 0.56 to 2.69 QALYs per patient. mSTR remained cost-effective (iNMB>0) compared with SOC in 78%, 85%, 91% and 92% of PSA simulations in Belarus, Georgia, Kazakhstan and Republic of Moldova, respectively, when compared with their country-level WTP threshold. Implementing mSTR in up to 80% of MDR/rifampicin-resistant TB patients may result in cost savings of $20.5, 2.5, 0.7 and 0.2 million in Kazakhstan, Belarus, Republic of Moldova and Georgia; equivalent to 17%, 3%, 4% and 1% of their national TB budgets, respectively.
CONCLUSIONS: Compared with SOC, mSTR is a more cost-effective treatment option for MDR/RR-TB, which should be considered by policymakers in the EECA region. Using insights from current implementations to scale up, plan operational changes and reallocate savings from mSTR could greatly enhance TB services and patient care.



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PMID: 41206134 [Indexed for MEDLINE]

Conflict of interest statement: Competing interests: None declared.

**57. Treatment Outcomes With an Oral Short Course Regimen for Rifampicin-resistant Tuberculosis in a High HIV Prevalence, Programmatic Setting in South Africa.**

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BACKGROUND: Bedaquiline-based oral short-course regimens (SCR) for rifampicin-resistant tuberculosis (RR-TB) are highly effective in clinical trials but outcomes in programmatic settings may be more modest. We evaluated clinical and bacteriological outcomes with a seven-drug, linezolid-containing SCR in a high-burden programmatic setting.
METHODS: This prospective cohort study enrolled adults with newly diagnosed RR-TB who were started on the oral SCR in the Eastern Cape Province, South Africa. The primary outcome was World Health Organization-defined end-of-treatment success. Secondary outcomes were TB-free survival (composite of alive, absence of a positive Mycobacterium tuberculosis culture, and treatment completed or in care) at 18 months and time to sputum culture conversion (SCC).
RESULTS: In total, 248 participants were included, 173 (69.8%) of whom were human immunodeficiency virus (HIV) positive. Culture conversion by 90 days was 96.8% (median time to SCC: 29 days, 95% confidence interval [CI]: 27-31). Treatment success was 37.5% (93/248). Reasons for unsuccessful treatment included switching to individualised regimens (35.1%, 87/248), loss to follow-up (19.4%, 48/348), and death (8.1%, 20/248). At 18 months, 157 (63.3%) participants achieved TB-free survival, with a cumulative mortality of 21.6% (95% CI: 16.1-29.0). Baseline 3+ smear (adjusted odds ratio [aOR]: 3.38, 95% CI: 1.28-8.95), higher age (aOR: 1.05, 1.01-1.08), and lower albumin (aOR: 0.94, 0.88-0.99), but not HIV status, were associated with unfavourable outcome at 18 months.
CONCLUSIONS: The oral SCR performed poorly in a high-burden TB programme. Strategies to support the implementation of effective new regimens for RR-TB are needed to translate outcomes from clinical trials into practice.



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PMID: 40342012 [Indexed for MEDLINE]

**58. Pulmonary tuberculosis in an immunocompromised patient: is it AIDS-related, COVID-19-associated, or both? A Case report.**

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BACKGROUND AND IMPORTANCE: Patients who are immunocompromised due to the HIV may
be more vulnerable to a severe coronavirus disease 2019 (COVID-19) infection and tuberculosis (TB) lung disease. The COVID-19 pandemic poses a serious hazard to TB sufferers.
CASE PRESENTATION: A 67-year-old black African homewife woman with an HIV/AIDS diagnosis arrived at the emergency room on 28 September 2022. The admitted woman had significant complaints, including muscle weakness, a loss of weight of about 33 pounds during the preceding week, headaches, and a cough. Reduced breath sounds were audible on chest auscultation in the right lower and upper lungs. She had two nasopharyngeal swabs for COVID-19 testing, which were positive. For the first five days of her stay in the hospital, she received continuous oxygen delivered through a nasal cannula at a rate of four liters per minute, and she is still taking her antiretroviral therapy (ART) regimen. For TB treatment, she took rifampicin 300 mg, isoniazid 600 mg, pyrazinamide 1600 mg, and ethambutol 1100 mg during a 2-month intensive phase, then rifampicin 225 mg and isoniazid 450 mg for a 4-month continuous phase.
CLINICAL DISCUSSION: COVID-19 may have a negative influence on TB control in a number of ways, including by accelerating the spread of the disease at the home, delaying TB diagnosis and treatment, worsening treatment outcomes, and raising the chance of acquiring drug-resistant TB. HIV-positive individuals are more likely to develop a TB infection. HIV impairs immunity, making it more difficult for the body to fight off mycobacterial TB germs.
CONCLUSION: According to the WHO Clinical Staging System Stage III of HIV/AIDS, the patient's COVID-19 infection and immunological impairment from HIV/AIDS both played a role in the development of pulmonary TB.

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PMID: 41180627

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**59. Emergence of novel sublineages of Mycobacterium tuberculosis in Pakistan.**

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INTRODUCTION: Understanding the distribution and prevalence of different M. tuberculosis lineages can help public health authorities and researchers track

the spread of tuberculosis (TB). Some lineages are thought to be more virulent, transmissible, and prone to drug resistance. Here, we sought to find the major lineages and sublineages of M. tuberculosis circulating in Pakistan.
METHODS: A total of 396 whole-genome sequencing datasets were retrieved from NCBI and TB research centers.
RESULTS: In the current study, only four lineages and 21 sublineages have been detected in 396 genomic isolates in which lineages 3 (n = 274/396, 69.19 %) was the predominant, followed by lineage 4 (77/396, 19.4 %), lineage 2 (31/396, 7.8 %), and lineage 1 (14/396, 3.5 %). Lineage 3 was the most common, in which sublineage 3.1.1 (n = 254/274, 93.79 %) was dominant, followed by sublineage 3.1.2.1 (n = 11/274, 4 %) and 3.1.2 (n = 8/274, 2.9 %). 8 sublineages are likely reported for the first time in Pakistan based on current genomic surveillance including sublineage 3.1.2.1 (n = 11/274, 4 %). There were 14 sublineages in lineage 4, of which sublineage L4.5 (23/77, 29.8 %) was the most common, followed by sublineage 4.9 (22/77, 28.5 %).
CONCLUSION: Collectively, these observations highlight Lineage 3's ability to acquire first-line drug resistance continued transmission. Its predominance in the current study highlights the urgent need for lineage-specific diagnostics, enhanced drug susceptibility testing and tailored therapeutic regimens. The detection of diverse Mtb sublineages, including L3.1.2.1 and various sublineages of L4 (e.g., 4.1.1.1, 4.1.2.1, 4.3.4.2, and 4.6.2.2), signifies advancement in understanding the genetic landscape of TB in the region.



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PMID: 41252803

**60. Discovery of Unprecedented Arylation Coupling Cyclopeptide Inspires Natural Product-like Antitubercular Lead Compounds.**

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Tuberculosis (TB) remains one of the world's deadliest communicable diseases. Naturally derived antibiotics appear frequently in nature as collections of structurally similar compounds representing an adaptive evolutionary response to drug resistance development. Herein, we report an undescribed versicomycin (1), featuring an unprecedented post-nonribosomal peptide synthetase (NRPS) assembly line-modified skeleton, which was isolated from the marine-derived fungus. Gram-scale total synthesis of versicomycin (1) was accomplished using a hybrid synthesis strategy combining solid-phase chemistry, solution-phase cyclization, and chemical C-H bond functionalization. Inspired by this undescribed natural product (NP) skeleton, we efficiently developed a compound library comprising 89 natural product-like cycloheptapeptides (2-90) bearing aryl groups. Their antituberculosis activity, structure-activity relationships (SARs), and conformational effects along with in vitro and in vivo antibacterial effects were evaluated using Mycobacterium marinum. Remarkably, CHNQD-02353 (21), the most potent candidate, suppressed the proliferation of Mycobacterium tuberculosis H37Ra effectively with an MIC90 value of 0.25 μM, which is 300-fold lower than that of versicomycin (1). The in vitro study demonstrated that CHNQD-02353 exhibited biocompatibility and synergistic effects with major frontline drugs, indicating its broad clinical application potential. Further subcutaneous M. marinum infection study in mice revealed that CHNQD-02353 cleared bacteria effectively from lesions, demonstrating its in vivo anti-infective potential. These results show that our integrated research strategy has discovered a structurally untapped chemical class, representing a promising new area for antibiotic drug discovery.



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PMID: 41169593

**61. Time to death and its associated factors among tuberculosis patients undergoing directly observed therapy at Butajira General Hospital: using accelerated failure time model.**

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INTRODUCTION: Tuberculosis (TB) remains a significant public health challenge, especially in resource-limited settings like Ethiopia, where the incidence is estimated at 151 cases per 100,000 population. Delays in diagnosis and treatment contribute substantially to TB-related morbidity and mortality. This study aimed to assess the time to death and identify key risk factors influencing mortality among TB patients receiving directly observed therapy (DOT) at Butajira General Hospital using a parametric survival approach.
METHODS: A retrospective cohort study was conducted among TB patients treated at Butajira General Hospital between September 2019 and August 2023. Survival analysis techniques including the Kaplan-Meier estimator, stratified Cox proportional hazards model, and the Accelerated Failure Time (AFT) model were employed to estimate survival time and identify factors associated with mortality.
RESULTS: Among 571 TB patients included in the study, 99 (17.3%) died during the follow-up period. The Weibull AFT model revealed that male sex (Φ = 0.75, 95% CI: 0.60-0.94, p = 0.015), age over 45 years (Φ = 0.70, 95% CI: 0.50-0.95, p = 0.030), HIV co-infection (Φ = 0.50, 95% CI: 0.35-0.72, p < 0.001), smoking (Φ = 0.60, 95% CI: 0.45-0.80, p < 0.001), multidrug-resistant TB, and working outside healthcare facilities (Φ = 0.70, 95% CI: 0.50-0.98, p = 0.040) were associated with accelerated time to death. In contrast, larger family size fewer than three members (Φ = 1.70, 95% CI: 1.20-2.42, p = 0.004) and more than three members (Φ = 2.50, 95% CI: 1.75-3.60, p = 0.001) as well as extrapulmonary TB (Φ = 1.80, 95% CI: 1.30-2.50, p = 0.001), smear-negative pulmonary TB (Φ = 1.60, 95% CI: 1.20-2.20, p = 0.005), and baseline weight over 35 kg (Φ = 1.90, 95% CI: 1.40-2.60, p < 0.001) were associated with longer survival time.
CONCLUSION: This study identified several significant predictors of TB-related mortality. Male sex, older age, HIV co-infection, smoking, multidrug-resistant TB (MDR-TB), and employment outside healthcare settings were associated with accelerated time to death. In contrast, better nutritional status, larger family support, and non-smear-positive TB types were linked to longer survival. The TB/HIV co-infection rate observed in this cohort exceeded the national average, highlighting the need for strengthened and integrated TB/HIV care. These findings can guide healthcare strategies, emphasizing the need for targeted interventions for high-risk groups and improving social support and healthcare access to enhance patient outcomes in TB management.



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PMID: 41214636 [Indexed for MEDLINE]

Conflict of interest statement: Declarations. Ethics approval and consent to participate: The study was approved from the department review board (DRB) of the Hawassa University department of statistics with reference number (Ref.No. Stat/060/15), which granted a waiver of informed consent given the retrospective nature of the study and the use of anonymized medical records. The information gathered from the patient file will be handled with confidence. The programming of data extraction tools avoids the display of names and other private information. The Declaration of Helsinki's guiding principles were followed during the study's execution. Consent for publication: Not applicable. No individual person's personal details, images, or videos are being used in this study. Competing interests: The authors declare no competing interests.

**62. Epetraborole pharmacokinetics/pharmacodynamics in the hollow fiber system model of Mycobacterium tuberculosis.**

Antimicrob Agents Chemother. 2025 Nov 5;69(11):e0048125. doi: 10.1128/aac.00481-25. Epub 2025 Sep 22.

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In the hollow fiber system model of tuberculosis (TB), the ratio of area under the concentration-time curve to MIC (AUC0-24/MIC) of 327.1 was identified as the epetraborole optimal exposure target for Mycobacterium tuberculosis kill. Monte Carlo simulation experiments showed that even the intravenous dose of 1,500 mg/twice daily would fail in the majority of patients, and the dose needed for good efficacy for TB may likely not be safe for patients.

DOI: 10.1128/aac.00481-25

PMCID: PMC12587543
PMID: 40980919 [Indexed for MEDLINE]

Conflict of interest statement: T.G. founded and served as the president and CEO of Praedicare Inc., a System of Systems Drug Development company, and founded Praedicare Africa, a clinical contract research organization. None of the other authors report any disclosures.

**63. Sterilizing activity of spectinamide MBX-4888A when replacing linezolid in the Nix-TB regimen in the relapsing BALB/c mouse model of tuberculosis.**

Antimicrob Agents Chemother. 2025 Nov 5;69(11):e0118325. doi: 10.1128/aac.01183-25. Epub 2025 Sep 30.

Peroutka-Bigus N(1), Scherman MS(1), Kaya F(2), Waidyarachchi SL(3), Liu J(4), Rushefsky JN(1), Butler MM(3), Bowlin T(3), Meibohm B(5), Gonzalez-Juarrero M(1), Lenaerts AJ(1), Zimmerman M(2), Lee RE(4), Robertson GT(1).

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Update of
bioRxiv. 2025 Aug 06:2025.08.04.668403. doi: 10.1101/2025.08.04.668403.

Spectinamides have garnered interest as experimental tuberculosis therapeutics owing to their safety profile and efficacy as partner agents when used in conjunction with established regimens in mice. The Nix-TB regimen of bedaquiline, pretomanid, and linezolid represents a short, effective regimen recommended for treatment of pre-extensively drug-resistant tuberculosis. However, linezolid administration is associated with severe adverse events that limit its use. Here we present preclinical data comparing Nix-TB regimens anchored by either linezolid or spectinamide MBX-4888A.

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PMCID: PMC12587623

PMID: 41025648 [Indexed for MEDLINE]

Conflict of interest statement: The authors declare no conflict of interest.

**64. Potent kinase inhibitors from the Merck KGaA OGHL: Novel hits against Trypanosoma brucei with potential for repurposing.**

PLoS Negl Trop Dis. 2025 Nov 11;19(11):e0013719. doi: 10.1371/journal.pntd.0013719. eCollection 2025 Nov.

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African trypanosomiasis remains a critical public health concern, with over 55 million people still at risk of infection. There are several issues associated with the current therapies including toxicity and resistance, which represent the main bottleneck of trypanosomiasis control. Thus, it is urgent to develop novel therapeutic tools with distinct mechanisms of action. The in vitro phenotypic screening of the Merck KGaA Darmstadt German Open Global Health Library (OGHL) against Trypanosoma brucei brucei yielded three potent kinase inhibitors belonging to different chemical series: a phenylcarbonylacrylamide (OGHL00006); a 2,4-di(phenylamino)pyrimidine (OGHL00133); and a 3-(triazol-4-yl)-7-azaindole (OGHL00169). They exhibited low micromolar to nanomolar median inhibitory concentrations (IC50 values of 0.6 μM, 0.007 μM, and 0.25 μM, respectively) and good selectivity when tested on Vero cells (SI > 2). OGHL00006 and OGHL00169 induced a rapid and irreversible growth arrest of T. b. brucei within 4-24 hours of incubation. Interestingly, these two hits have also been reported to display antiplasmodial and/or anthelminthic activities, hinting at a similar mechanism of action across multiple species. Given the significant sequence similarities between the human and trypanosome kinomes, we rationalized the putative mechanisms of action for the identified hits through comparative modeling of protein-ligand complexes. This study suggests promising avenues for drug and/or target repurposing against trypanosomiasis.

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PMID: 41218070 [Indexed for MEDLINE]

Conflict of interest statement: The authors have declared that no competing interests exist.

**65. Discrepancies in isoniazid susceptibility profiles: Bactec MGIT 960-resistant but GenoType MTBDRplus-susceptible Mycobacterium tuberculosis strains in Hunan, China.**

Microbiol Spectr. 2025 Nov 4;13(11):e0110125. doi: 10.1128/spectrum.01101-25. Epub 2025 Oct 1.

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Discordant drug susceptibility testing (DST) results between the Bactec MGIT 960 system (MGIT) and the GenoType MTBDRplus assay (MTBDRplus) for isoniazid (INH) complicate clinical decision-making. In this study, we performed minimum inhibitory concentration (MIC) assays and whole-genome sequencing (WGS) on 53 Mycobacterium tuberculosis strains identified as INH-resistant by MGIT but INH-susceptible by MTBDRplus. The variants conferring INH resistance were evaluated by the WHO mutation catalogue. Our results showed that only five strains carried variants classified as "associated with resistance" (Group 1/2), including katG Trp39STOP, katG Ser315Asn, inhA -154G>A, and inhA Ser94Ala. In addition, 44 strains carried 70 variants classified as "Group 3: Uncertain significance" across nine genes, including katG, ahpC, inhA, Rv0010c, Rv1129c, Rv2752c, mshA, dnaA, and Rv1258c. The remaining four strains carried no variants (Groups 1-3) linked to INH resistance. No significant difference in the prevalence of high-level INH resistance was observed between lineage 2 and lineage 4 strains ($\chi^2 = 0.232$, $P = 0.630$). Our findings indicate that the variants classified as "uncertain significance" may be the main genetic determinants causing discordant results, highlighting their associations with INH resistance that need to be further investigated.

IMPORTANCE: This study addresses a critical challenge in drug susceptibility testing (DST): the discrepancies in DST results for isoniazid (INH) between the Bactec MGIT 960 system and the GenoType MTBDRplus assay. These discordant results significantly complicate treatment decisions, potentially leading to suboptimal patient outcomes. Using MIC assays and WGS on 53 clinical Mycobacterium tuberculosis strains, we provide valuable insights into the genetic basis of INH resistance. Our findings showed that only a small fraction of strains carried variants definitively linked to INH resistance, while a larger number harbored variants of uncertain significance across multiple genes, underscoring the complexity of INH resistance mechanisms. This study highlights the urgent need to refine our understanding of these "Group 3: uncertain significance" variants, as they appear to be a primary driver of the discrepancies. Additionally, this study emphasizes the importance of integrating advanced sequencing tools into DST to improve the accuracy of INH resistance detection.

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PMID: 41031815 [Indexed for MEDLINE]

Conflict of interest statement: The authors declare no conflict of interest.

**66. Design and synthesis of isoxazole-functionalized benzene sulphonamides as novel inhibitors of Mycobacterium tuberculosis β-carbonic anhydrases.**

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The escalating prevalence of multidrug-resistant tuberculosis (MDR-TB) underscores the urgent need for new classes of antitubercular agents targeting novel pathways. Carbonic anhydrase, a ubiquitous metalloenzyme, catalyses the reversible hydration of carbon dioxide in the CO2 + H2O ⇋ HCO3 - + H+ reaction. Suppressing this enzymatic activity has recently been identified as a new pathway for the treatment of Mycobacterium tuberculosis. To address this, a series of isoxazole-sulphonamides was rationally designed, incorporating an isoxazole pharmacophore as the aromatic tail, amide as a linker, and sulphonamide as the zinc-binding group. These compounds were evaluated against Mycobacterium tuberculosis carbonic anhydrases (MtCA 1 and 3) and two human carbonic anhydrases (hCA I and II) to identify selective inhibitors of the bacterial enzymes. The findings indicated that molecules containing an isoxazole pharmacophore with amide-linked benzene-3-sulphonamide were significantly more selective for MtCA 3 than hCA I and II. Among these compounds, 12c, 12e, and 19b had the highest inhibition against the MtCA 3 with K i values between 0.08-0.09 μM compared to the standard acetazolamide with a K i value of 0.10 μM. Some of the best compounds exhibited potent and selective inhibition of MtCA 3 over hCA I and II, with the meta- and para-substituted derivatives demonstrating higher selectivity and stronger inhibition. Specifically, compound 19b proved to be 199 and 38 times more selective for MtCA 3 than hCA I and hCA II respectively, compared to the standard drug acetazolamide, which is a non-selective CA inhibitor. The potential of compound 19b as a promising antitubercular agent with a MIC value of 8 μg mL-1 against mc2 6230 was further strengthened by in silico ligand-target interaction studies. Thus, compound 19b is emphasised as a promising lead in the pursuit of new, selective agents targeting MtCA 3.



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PMID: 41209293

Conflict of interest statement: The authors declare no conflict of interest.

**67. Prospects and Research Trends of Tuberculosis in Iran: A Bibliometric Study With a Science Mapping Approach.**

Interdiscip Perspect Infect Dis. 2025 Oct 31;2025:7594073. doi: 10.1155/ipid/7594073. eCollection 2025.

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BACKGROUND: Tuberculosis (TB), as one of the challenges of the health system in Iran, is of interest to Iranian researchers. It is necessary to present the research perspective of the research in this field to guide the future research. The aim of this research is bibliometric and citation study and providing a scientific map of TB research in Iran.
METHODS: This bibliometric and cross-sectional analyzes the research outputs of the subject area of TB indexed in the Scopus database up to 2024. SciMAT and VOSviewer software were used to visualize and predict the trends in research on the topic.
RESULTS: The most scientific productions occurred in the years 2020-2022 as well as 2016, and the research density was low in these years. Isoniazid and rifampicin were the most frequent topics in TB researches. In terms of average citations, diabetes mellitus had the most citations. Multidrug-resistant TB, diseases and complications, signs and symptoms, diagnosis and epidemiology of TB, and immunological and genetic studies related to TB are three research lines in TB research.
CONCLUSION: TB research in Iran is expanding both quantitatively and in terms of research concepts. Thematic maps and strategic diagrams were presented. Paying attention to themes and strategic diagrams in the research decision-making of TB researchers in Iran in order to conduct effective research is helpful. Also, subject specialists in various fields of TB can obtain a specific research perspective based on the maps and indicators provided.



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PMID: 41210929

Conflict of interest statement: The authors declare no conflicts of interest.

**68. Protocol for the development of a Core Outcome Set (COS) for reporting outcomes of clinical trials of anti-tuberculosis treatment in adults with pulmonary Tuberculosis.**

Trials. 2025 Nov 18;26(1):521. doi: 10.1186/s13063-025-09224-8.

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BACKGROUND: The global burden of tuberculosis (TB) remains high, and treatment of both drug-susceptible and drug-resistant diseases is complex and prolonged. International clinical trial networks and public-private partnerships are beginning to deliver advances in TB treatment, and collaborative data-sharing efforts are being promoted to improve the transparency and scrutiny of the evidence used in formulating treatment guidelines and public health policies. Empirical studies have identified variability in the selection and reporting of clinical trial outcomes in historical and recent phase III trial reports and protocols in TB. This variability could affect the synthesis of evidence and interpretation by practitioners, regulators, and policymakers.
METHODS AND ANALYSIS: A comprehensive list of outcomes used in phase III treatment trials of pulmonary TB in adults, grouped according to key domains, will be identified from systematic reviews of published trials and trial protocols. A systematic review of qualitative evidence will inform outcomes important to people diagnosed with TB. Consensus will be sought from an international panel of participants representing key stakeholder groups using a multi-stage Delphi process. The final COS identified from the Delphi survey will be ratified at an online consensus meeting and approved by the SSC. The process will be conducted according to the Core Outcome Set-STAndards for Development (COS-STAD) guidance and with the support of the Core Outcome Measures in Effectiveness Trials (COMET) Initiative.
DISCUSSION: A COS implemented in the TB trials community that reflects the outcomes most important to stakeholders would help ensure that important evidence is translated rapidly, clearly, and effectively into practice to maximise patient benefit.
TRIAL REGISTRATION: The study has been registered with the COMET database of core outcome sets (study 2195, registered October 2022).

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PMCID: PMC12625417
PMID: 41254665 [Indexed for MEDLINE]

Conflict of interest statement: Declarations. Ethics approval and consent to participate: Ethics approval has been granted by the Institute of Population Health Research Ethics Committee (ref 12253). Written informed consent is a requirement for participant registration. The results of the Core Outcome Set (COS) process and recommendations will be shared with participants and stakeholder groups, including prominent clinical trial sponsors and networks, published in a peer-reviewed scientific manuscript, and disseminated at relevant international research meetings. Consent for publication: Not applicable. Competing interests: The authors declare that they have no competing interests. All steering committee members and participants will be asked to declare any relevant conflicts of interest before participating in the process. No conflicts of interest have been made by members of the study steering committee that precludes further participation in the process.

**69. Effects of zinc carnosine on bone loss in mice with diabetic osteoporosis.**

Mol Med Rep. 2026 Jan;33(1):13. doi: 10.3892/mmr.2025.13723. Epub 2025 Oct 31.

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Diabetic osteoporosis (DOP) is on the rise globally, presenting a notable healthcare challenge due to its complex pathogenesis and high fracture risk. Currently, available treatments have limitations, highlighting an urgent need for novel therapeutic approaches. Zinc carnosine (ZnC), a compound formed by the chelation of carnosine with trace-element zinc ions, has shown potential in

inhibiting the accumulation of advanced glycation end products in the bone microenvironment, yet its effects on DOP remain under-explored. The present study aimed to examine the effects of ZnC on bone loss in a mouse model of DOP. A total of 24 male mice, aged 6 weeks, were assigned to control, type 2 diabetes mellitus (T2DM) and ZnC intervention groups. DOP was induced using a high-fat diet combined with streptozotocin (STZ). Following 8 weeks of treatment with ZnC at a dosage of 100 mg/kg/day, bone parameters were evaluated using micro-computed tomography (micro-CT), histological staining and molecular analyses. The micro-CT analysis revealed that bone mineral density (BMD), bone volume/tissue volume (BV/TV), number of bone trabeculae (Tb.N), thickness of cortical bone (Ct.Th) and area of cortical bone (Ct.Ar) were significantly lower in the T2DM model group compared with that in the control group ($P<0.05$). Conversely, bone trabecular separation (Tb.Sp) structural model index (SMI) and porosity of cortical bone (Ct.Po) were significantly higher in the T2DM model group compared with those in the control group ($P<0.05$). The ZnC intervention group showed significant increases in BMD, BV/TV, Tb.N, Ct.Th and Ct.Ar, and significant decreases in Tb.Sp compared with the T2DM model group. Tartrate-resistant acid phosphatase staining demonstrated a notable reduction in osteoclast numbers in the ZnC intervention group relative to the T2DM model group. Furthermore, immunohistochemical staining and reverse transcription-quantitative PCR indicated an upregulation of osteoblastic markers, including type Ⅰ collagen, osteocalcin and osteoprotegerin, alongside a downregulation of the osteoclastic marker receptor activator of nuclear factor-κB ligand in the ZnC group. In conclusion, ZnC supplementation was shown to mitigate bone loss in DOP by promoting bone formation and reducing bone resorption. This was evidenced by enhancements in bone microstructure, a reduction in osteoclast activity and favorable changes in bone metabolism markers. These findings underscore the potential of ZnC as a therapeutic option for bone diseases associated with diabetes.

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PMID: 41170739 [Indexed for MEDLINE]

Conflict of interest statement: The authors declare that they have no competing interests.

**70. Synthesis and characterization of core-shell mussel inspired magnetic molecularly imprinted polymer nanoparticles for the solid phase extraction of levofloxacin in human plasma.**

BMC Chem. 2025 Oct 22;19(1):280. doi: 10.1186/s13065-025-01641-9.

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Determination of pharmaceuticals in biological matrices is crucial for pharmaceutical development, toxicological studies, and therapeutic drug monitoring. Accurate quantification of drugs in plasma requires reliable analytical techniques; however, the complexity of biological fluids hinders direct analysis without an effective sample preparation step. In this study, $Fe_3O_4$ was synthesized using mussel-inspired magnetic molecularly imprinted polymer nanoparticles (MIP NPs) through a single-step auto-polymerization process with levofloxacin as the template and methyldopa as the monomer. The integration of $Fe_3O_4$ core synthesis, self-polymerization, and molecular imprinting in a single step provides a unique and streamlined methodology, reducing fabrication complexity and time. The prepared $Fe_3O_4$@MIP NPs were successfully applied to extract levofloxacin from spiked human plasma. UV-spectroscopy studies confirmed selective recognition, binding efficiency, and optimization of recovery conditions, achieving approximately 93.5% recovery. The $Fe_3O_4$@MIP NPs demonstrated significant imprinting capability and high adsorption capacity. This approach offers a novel and cost-effective platform for rapid, selective drug extraction from complex biological matrices, with direct clinical relevance for therapeutic drug monitoring of levofloxacin in multidrug-resistant tuberculosis, particularly suited for resource-limited settings.



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PMID: 41126269

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publication: Not applicable. Competing interests: The authors declare no competing interests.

**71. In vitro exposure to clofazimine can select for delamanid and pretomanid resistance in Mycobacterium tuberculosis.**

Antimicrob Agents Chemother. 2025 Nov 5;69(11):e0111325. doi: 10.1128/aac.01113-25. Epub 2025 Sep 22.

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In vitro experiments with Mycobacterium tuberculosis showed that clofazimine exposure selected for delamanid and pretomanid resistance and mutations in fbiA, fbiC, or fbiD-after the acquisition of Rv0678 mutations where this could be determined. Whether this is also possible in vivo and in an Rv0678 wild-type background has to be studied further. Based on the available evidence, however, we propose that nitroimidazole resistance should not be considered an exclusion criterion for the use of clofazimine.

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PMCID: PMC12587575
PMID: 40980917 [Indexed for MEDLINE]

Conflict of interest statement: C.U.K. is a consultant for the TB Alliance and worked as a consultant for FIND, the Stop TB Partnership, the WHO Global TB Programme, and WHO Regional Office for Europe. C.U.K.'s past consulting for Becton Dickinson involved a collaboration with Janssen and Thermo Fisher Scientific. C.U.K. collaborated with PZA Innovation and is or was an unpaid advisor to Bigtec Labs, Cepheid, and Genoscreen; GenoScreen covered related travel and accommodation expenses only. All other authors have no conflict of interest to report.

**72. Tuberculous Meningitis With Paradoxical Reaction in an Immunocompetent Young Male Treated by Interleukin-1 Receptor Antagonist.**

Case Rep Infect Dis. 2025 Nov 3;2025:8891508. doi: 10.1155/crdi/8891508. eCollection 2025.

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A 22-year-old man presented with headache, night sweats, intermittent fever, tremors, sleep disturbances, agitation, and hallucinations for 2 months. Thoracic computed tomography (CT) showed widespread interstitial nodular lesions, but initial cranial CT showed no significant pathology. Cerebrospinal fluid (CSF) analysis revealed 25 cells/mm3 of white blood cells (72% neutrophils), 83 mg/dL protein, and 30 mg/dL glucose (concurrent serum glucose was 103 mg/dL). Gram and Ziehl-Neelsen stains were negative for acid-fast bacilli. Tuberculosis (TB) cultures and Mycobacterium PCR tests remained negative. Biopsy of the bronchoalveolar lavage sample showed necrotizing granulomatous inflammation, and the Mycobacterium tuberculosis PCR result was positive. During the first month of first-line anti-TB treatment, the patient experienced recurrent severe headaches, persistent fever, and decreased visual acuity. Contrast-enhanced MRI revealed lesions that were consistent with tuberculous meningitis (TBM). Considering the possibility of drug-resistant TB,

streptomycin 1 gr/qd (quaque die) intramuscularly and linezolid 600 mg/bid (bid in die) intravenously were added to the regimen. The patient's symptoms persisted during the second month of treatment. The patient experienced epileptic seizures. The control MRI showed an enlargement of the lesions. A paradoxical reaction was considered. Intravenous methylprednisolone 500 mg/day was initiated. The patient did not respond clinically, and his complaints continued. The patient was started on the IL-1 inhibitor anakinra. Paradoxical inflammatory reactions are common in TBM but challenging to predict. When severe, they can lead to significant neurological morbidity and death. This article aimed to share a case that did not respond to corticosteroids, a standard treatment for paradoxical reactions, but was successfully managed with the IL-1 inhibitor anakinra.



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PMID: 41221143

Conflict of interest statement: The authors declare no conflicts of interest.

**73. Pulmonary Tuberculosis with Polyclonal Infection - Diagnostic Challenges and the Importance of Sequencing to the Improvement of Case Management - Case Report.**

Infect Drug Resist. 2025 Nov 1;18:5653-5660. doi: 10.2147/IDR.S554050. eCollection 2025.

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Many studies on the molecular epidemiology of tuberculosis (TB) have shown that 10-20% of patients may be infected with more than one strain of Mycobacterium tuberculosis (MTB), during a single episode of the disease. However, data on the frequency of this phenomenon are underestimated, and methodological difficulties mean that most cases are not detected. Below we present the first case of polyclonal/mixed infection documented in Poland. We described the case of a 33-year-old Ukrainian man, imprisoned in a Polish prison, who was diagnosed with pulmonary TB confirmed by culture. During the 6-month therapy, the patient was treated in three Polish hospitals, but no negative sputum test result was

obtained. In the course of microbiological and molecular diagnostics, conducted from June 2021 to February 2022, divergent results were obtained from drug susceptibility testing and genotyping of MTB strains isolated from clinical materials from the patient. In the final stage of the tests, it was confirmed that the patient was infected with two strains of MTB - one of them was drug-sensitive and belonged to the T1 267 genotype, the other was pre-extensively drug resistant (pre-XDR) and belonged to the Beijing 265 genotype. The existence of clonally complex TB infections resulting in heteroresistance to basic antituberculosis drugs has important implications for patient care. Established molecular methods complemented by routine microbiological diagnostics allow rapid detection of these infections and appropriate adjustment of therapy.



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PMCID: PMC12587859
PMID: 41199939

Conflict of interest statement: The authors declare no conflicts of interest in this work.

**74. Prevalence and Correlates of Hyperglycemia Among People Living With HIV and TB on Dolutegravir-Based Antiretroviral Therapy in Zimbabwe: A Cross-Sectional Study.**

Health Sci Rep. 2025 Nov 9;8(11):e71480. doi: 10.1002/hsr2.71480. eCollection 2025 Nov.

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BACKGROUND AND AIMS: In low- and middle-income countries, dolutegravir-based antiretroviral therapy regimens are the preferred first-line treatment for adults, adolescents, and children with human immunodeficiency virus (HIV). Dolutegravir exhibits a higher genetic barrier to resistance, improved tolerability, and reduced potential for drug-drug interactions. However, emerging reports suggest a possible association between dolutegravir usage and hyperglycemia. Therefore, this study aims to investigate the hyperglycemia risk in dolutegravir-based antiretroviral therapy among people living with HIV and tuberculosis (TB) in Zimbabwe.
METHODS: An analytical cross-sectional study was conducted on 162 participants aged 18 and older, recruited from April to July 2024 in Harare, Zimbabwe. Participants were divided into three groups based on their HIV and TB status and dolutegravir dosage. Participants' glycated hemoglobin levels were analyzed to determine the hyperglycaemic risk. A questionnaire was also administered to assess the risk factors associated with hyperglycemia. The R statistical software (version 4.3.2, Vienna, Austria) was used for data analysis. A p-value of $< 0.05$ was considered to be statistically significant.
RESULTS: The median (interquartile range) ages for these sub-groups were 44 [36-56], 44 (29.3-54.8), and 45 [35-56] years, respectively, and the age range was 20-80 years. The group taking 100 mg of dolutegravir had a 40% prevalence of impaired glucose regulation, and a hyperglycemia prevalence of 31%. In the multivariable logistic regression analysis, taking 100 mg of dolutegravir was associated with a 5.17 (95% Confidence Interval: 1.21-27.82) fold risk of developing hyperglycemia.
CONCLUSION: The study findings indicate that the prevalence of hyperglycemia and impaired glucose regulation is high in patients taking dolutegravir-based antiretroviral therapy in Zimbabwe. People living with both HIV and TB taking a double dose of dolutegravir are at a higher risk of hyperglycemia and impaired glucose regulation than those taking lower doses. This emphasizes the necessity for clinical and public health interventions to mitigate this emerging hyperglycaemic risk.



DOI: 10.1002/hsr2.71480
PMCID: PMC12598190
PMID: 41221425

Conflict of interest statement: The authors declare no conflicts of interest.

**75. Arabidopsis root defense barriers support beneficial interactions with**

**rhizobacterium Pseudomonas simiae WCS417.**

New Phytol. 2025 Nov;248(4):2021-2039. doi: 10.1111/nph.70549. Epub 2025 Sep 4.

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Plant roots interact with pathogenic and beneficial microbes in the soil. While root defense barriers block pathogens, their roles in facilitating beneficial plant-microbe associations are understudied. Here, we examined the impact of specific root defense barriers on the well-known beneficial association between Arabidopsis thaliana and the plant growth-promoting rhizobacterium Pseudomonas simiae WCS417. Using 15 Arabidopsis mutants with alterations in structural (cutin, suberin, callose, and lignin) and chemical (camalexin and glucosinolates) defense barriers, we demonstrate that some barriers impact WCS417-mediated plant growth responses and its root colonization. Root exudates from Arabidopsis wild-type (WT) and mutant plants differentially affected the WCS417 transcriptome, with camalexin notably impacting bacterial motility and chemotaxis, which was also confirmed by in vitro studies. On the plant side, WCS417-induced transcriptome changes in the roots of defense barrier mutants were significantly different from those in WT plants, particularly affecting growth and defense-related processes. Specifically, the data indicated altered activity of reactive oxygen species in several of the defense barrier mutants, which was confirmed in planta. Our data suggest that various root defense barriers play a role in balancing growth and defense during this mutualistic interaction, thereby impacting the establishment and effectiveness of plant mutualists, extending their established role in disease resistance.



DOI: 10.1111/nph.70549
PMCID: PMC12529037

PMID: 40906614 [Indexed for MEDLINE]

Conflict of interest statement: None declared.

**76. Critical appraisal of progress and challenges in tuberculosis preventive treatment in the Western Pacific Region: a situational analysis of seven high tuberculosis burden countries.**

Trop Med Health. 2025 Oct 27;53(1):143. doi: 10.1186/s41182-025-00840-3.

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We commend Oh et al.'s recent analysis of TB preventive treatment (TPT) in the Western Pacific Region, but note important gaps and ways forward. We first caution that reliance on routine program data may overestimate gains. For example, China's passive surveillance misses ≈20% of cases [1]. Prospective cohorts or integrated surveillance including clinical databases could validate coverage estimates. We also urge attention to overlooked risk groups beyond children and PLHIV (as highlighted by Oh et al. [2]), groups like healthcare workers, prisoners, and people with diabetes warrant targeted TPT pilots (e.g., occupational health or prison-based programs). In the Philippines, ~ 36% of TB patients first seek private care [3], so partnering with private clinics and pharmacies is essential to reach all contacts. Likewise, MDR-TB contacts were underemphasized; WHO now strongly recommends a 6-month levofloxacin regimen for MDR contacts [4]. We encourage pilot studies of this regimen (as in Mongolia [5]) and operational research on MDR-TPT. Finally, policy does not guarantee practice as Cambodia and Lao PDR have guidelines, yet stockouts and training gaps persist [6, 7]. Embedding TPT in universal health insurance and conducting cost effectiveness studies will support sustainable scale-up. In sum, by suggesting concrete examples and research strategies for each country, we aim to refine Oh et al.'s insights into actionable steps for TPT acceleration.



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**77. TOAST: a novel tool for designing targeted gene amplicons and an optimised set of primers for high-throughput sequencing in tuberculosis genomic studies.**

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BACKGROUND: Amplicon sequencing of Mycobacterium tuberculosis resistance-associated genes offers a cost-effective alternative to whole-genome sequencing for rapid profiling of infections and guiding clinical management. However, existing assays require frequent manual updates to accommodate emerging resistance mutations, limiting scalability and responsiveness.
RESULTS: We present TOAST (Tuberculosis Optimised Amplicon Sequencing Tool), a novel software tool that automates primer design by integrating mutation frequencies from a curated database of over 68,000 drug-resistant M.

tuberculosis genomes. TOAST prioritises regions with the highest clinical relevance, accounting for single-nucleotide polymorphisms, insertions, and deletions. The software supports customisation of design parameters such as amplicon length, melting temperature, and GC content, while screening for undesirable primer properties, including self-dimers and off-target binding. Using TOAST, we designed a multiplex panel of 33 amplicons targeting mutations associated with resistance to 13 anti-TB drugs. These amplicons covered over 97% of resistance mutations in a 68 K isolate database and were validated using Oxford Nanopore sequencing of two clinical samples, achieving high uniform coverage with a minimum sequencing depth exceeding 50-fold across all targets. CONCLUSIONS: TOAST represents a major advancement in targeted TB sequencing by integrating large-scale clinical genomic data directly into assay design. This enables rapid, high-coverage, and adaptable amplicon sequencing, enhancing diagnostic precision and surveillance capabilities for drug-resistant TB. TOAST's framework is also extensible to other pathogens, supporting broader applications in infectious disease genomics. SUPPLEMENTARY INFORMATION: The online version contains supplementary material available at 10.1186/s12864-025-12247-9.

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**78. Sequestration and suppressed synthesis of oncogenic HMGA1 using engineered adenoviruses decreases human pancreatic and breast cancer cell characteristics.**

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HMGA1, an architectural transcription factor that plays a crucial role in tumorigenesis, chemotherapy resistance and cancer stem cell transformation in many human cancers, is intrinsically disordered and cannot be targeted by conventional small molecule drug therapy. While HMGA1 is required and essential for normal growth and development, HMGA1 expression occurs at very low levels in normal healthy adult cells. In contrast, HMGA1 is expressed at very high levels in many different types of human cancer cells. Since HMGA1 cannot be targeted using conventional small molecule drug therapy, alternative approaches are needed to target HMGA1 in new cancer therapies. Here, we explored the use of serotype 5 adenoviruses (Ad5) engineered 1) to sequester overexpressed HMGA1 in cancer cells using an HMGA1 hyper binding site (HBS) inserted into the Ad5 genome and 2) to suppress HMGA1 synthesis in cancer cells by incorporating exogenous genes into the Ad5 genome that encode an artificial HMGA1 cis-antisense transcript (AAT) and that encode a gene to express an HMGA1-targeted shRNA transcript (shRNA). The three engineered Ad5s were tested in MiaPaCa-2, PANC-1 and BxPC-3 human pancreatic cancer cell lines and in the ZR-75 human breast cancer cell line. Cancer cell viabilities and cell migration capability decreased by ~50-75% with HBS viruses and by 25-50% for shRNA and AAT viruses. Anchorage-independent migration capacity decreased by 60-70% with all three HBS, shRNA and AAT viruses. HMGA1 mRNA transcripts levels varied from 100 to 300 copies per cell in untreated cells and these levels were not significantly affected by treatment with the HBS and shRNA viruses, however the HMGA1 mRNA levels increased by ~3-fold upon AAT virus treatment. HMGA1 protein levels decreased in the range of 40, 50 and 70% with shRNA, AAT and HBS viruses, respectively. The HBS virus designed to sequester HMGA1 proved most effective overall in suppressing HMGA1 oncogenic activity in these in vitro cell-based studies compared to the AAT and shRNA viruses.



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**79. Estimating homeostasis model assessment for insulin secretion by using multiple adaptive regression spline in healthy Taiwanese men.**

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The prevalence of type 2 diabetes (T2M) has been increasing drastically in recent two decades. One of the main underlying pathophysiology was decreased insulin secretion (ISEC). Even though there were many studies found the related factors affecting ISEC, no study used multiple adaptive regression spline (MARS) to build an equation estimating ISEC. In the present study, we used MARS to estimate hemostasis assessment model of β-cell (HOMA-β) in healthy Taiwanese men. Totally, there were 317 men enrolled. Participants who were taking medications related to metabolic syndrome were excluded. MARS was used to build

an equation to estimate HOMA-β. Multiple linear regression (MLR) was taken as a bench mark for comparing the accuracy with MARS. The method with less estimation errors was considered to be more accurate. All the estimation errors were smaller for MARS. This indicated that MARS outperformed MLR. The equation built is shown below. The r2 of this equation was 0.58. By using MARS, we built an equation which could accurately estimate HOMA-β in a healthy Taiwanese men cohort. The most important factor was HB, followed by TB, education level, sport area, GOT, GPT, and BF. This equation has a practical clinical use and could further explore which were the factors that were related to ISEC.



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## Recent TB News

**MIT study finds targets for a new tuberculosis vaccine**
https://news.mit.edu/2025/mit-study-finds-targets-new-tuberculosis-vaccine-1105

After a large-scale screening of tuberculosis proteins, MIT engineers were able to identify immunogenic peptides that could stimulate a strong response from a type of T cells that are responsible for creating an immune response to TB infection. The goal is to use these newly found peptides and create a vaccine that could work for most people, as there is still a large TB burden globally.

**TB cases fall for first time since pandemic**
https://news.un.org/en/story/2025/11/1166349

For the first time since the COVID-19 pandemic, TB cases are decreasing. However, while progress has been made globally, funding gaps pose a threat to this progress. The WHO shares that while there are declines in the global burden of TB as well as progress in TB testing, treatment, and research, it is projected that funding cuts could cause up to 2 million more deaths and 10 million more cases within the next decade.

**Phase II data suggest new drug could unlock shorter TB treatment**
https://www.cidrap.umn.edu/tuberculosis/phase-2-data-suggest-new-drug-could-unlock-shorter-tb-treatment

New data from a phase II trial showed that sorfequiline showed greater activity against drug-susceptible TB compared to existing treatments at 8 weeks in addition to a more favorable safety profile. These results also demonstrated enough evidence to move into a phase III trial which is planned to be tested in both drug susceptible and drug resistant TB patients, giving hope for a new, shorter treatment for many suffering from TB.