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1. Global burden of MDR-TB and XDR-TB: trends, inequities, and future implications for public health planning.

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BACKGROUND: Drug-resistant tuberculosis (TB) remains a major global health threat, reflecting disparities in healthcare capacity, access, and socioeconomic development. Previous research often lacks geographic breadth. This study

provides a comprehensive assessment of the global, regional, and national burden of Multidrug-resistant TB without extensive drug resistance (MDR-TB) and extensively drug-resistant TB(XDR-TB) from in Global Burden of Disease Study (GBD) 2021 Study 1990 to 2021, with a focus on distributional inequities. The findings aim to guide resource prioritization, inform targeted interventions, and reduce the burden in high-risk populations.
METHODS: We systematically assessed the global, regional, and national burden of MDR-TB and XDR-TB, along with their change trends from 1990 to 2021, using data from the GBD 2021 database. The indicators included age-standardized incidence rate (ASIR), prevalence rate (ASPR), mortality rate (ASMR), and disability-adjusted life-years rate (ASDR). ASDR was analyzed in conjunction with the sociodemographic index (SDI) for a comprehensive assessment. Health inequalities were quantified using the slope index of inequality (SII) and concentration index (CCI). Frontier analysis estimated the achievable outcomes across different development levels, while decomposition analysis identified the key factors driving changes in disease burden.
RESULTS: In 2021, the global ASIR of MDR-TB was 5.42 per 100,000 population [95% uncertainty interval(UI): 3.17, 9.34]), and the ASIR of XDR-TB was 0.29 per 100,000 population (95% UI: 0.21, 0.42). From 1990 to 2021, the ASIR of MDR-TB [AAPC = 0.14%, 95% confidence interval (CI): 0.13, 0.14] and XDR-TB (AAPC = 0.01%, 95% CI: 0.01, 0.02) both showed an increasing trend. The ASIR and ASMR of MDR-TB increased in low and low-middle SDI regions. Similarly, the ASIR and ASMR of XDR-TB increased in all five SDI regions. The ASIR of MDR-TB increased in 155 countries, with the largest increase observed in Somalia (AAPC = 1.79%, 95% CI: 1.67, 1.92). The ASIR of XDR-TB increased in all countries. From 1990 to 2021, both absolute and relative health inequalities in the ASDR of MDR-TB and XDR-TB have grown. In addition, the ASIR and incidence of MDR-TB and XDR-TB are negatively correlated with SDI.
CONCLUSION: The burden of MDR-TB/XIDR-TB is projected to increase, with persistent disparities concentrated in low-SDI settings. Targeted public health strategies-including improved resource allocation, infrastructure development, and community health education-are essential to reduce inequities. Strengthening these efforts may enhance global TB control and advance progress toward health equity.

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University of Washington (No. STUDY00009060). All the information about ethical standards is available through the official website (http://www.healthdata.org/gbd/2021). Consent for publication: Not applicable. Competing interests: The authors declare no competing interests.

2. Using Machine Learning Methods to Predict Early Treatment Outcomes for Multidrug-Resistant or Rifampicin-Resistant Tuberculosis to Enhance Patient Cure Rates: Development and Validation of Multiple Models.

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BACKGROUND: Early prediction of treatment outcomes for patients with multidrug-resistant or rifampicin-resistant tuberculosis (MDR/RR-TB) undergoing extended therapy is crucial for enhancing clinical prognoses and preventing the transmission of this deadly disease. However, the absence of validated predictive models remains a significant challenge.
OBJECTIVE: This study compared a conventional logistic regression model with machine learning (ML) models using demographic and clinical data to predict outcomes at 2 and 6 months of treatment for MDR/RR-TB. The goal was to advance model applications, refine control strategies, and boost MDR/RR-TB cure rates.
METHODS: This retrospective study encompassed an internal cohort of 744 patients with MDR/RR-TB examined between January 2017 and June 2023, as well as an external cohort comprising 137 patients with MDR/RR-TB examined between March 2021 and June 2022. Data on culture conversion were collected at 2 and 6 months, and culture conversion was tracked in the external cohort at the same time

points. The internal cohort was assigned as the training set, whereas the external cohort was used as the validation set. Logistic regression and 7 ML models were developed to predict the culture conversion of patients with MDR/RR-TB at 2 and 6 months of treatment. Model performance was evaluated using the area under the curve, accuracy, sensitivity, and specificity.
RESULTS: In the internal cohort, culture conversion rates for MDR/RR-TB were 81.9% (485/592) at 2 months and 87.1% (406/466) at 6 months. The odds ratio for treatment success was 8.55 (95% CI 3.31-22.08) at 2 months and 20.33 (95% CI 6.90-59.86) at 6 months after conversion, with sensitivities of 86.5% and 92.2% and specificities of 57.1% and 63.2%, respectively. The artificial neural network model was the best for culture conversion at both 2 and 6 months of treatment, with areas under the curve of 0.82 (95% CI 0.77-0.86) and 0.90 (95% CI 0.86-0.93), respectively. The accuracy, sensitivity, and specificity of the model were 0.74, 0.74, and 0.75 at 2 months of treatment and 0.80, 0.79, and 0.87 at 6 months of treatment, respectively.
CONCLUSIONS: The ML models based on 2- and 6-month culture conversion could accurately predict treatment outcomes for patients with MDR/RR-TB. ML models, particularly the artificial neural network model, outperformed the logistic regression model in both stability and generalizability and offer a rapid and effective tool for evaluating therapeutic efficacy in the early stages of MDR/RR-TB treatment.

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3. Targeting G1-S-checkpoint-compromised cancers with cyclin A/B RxL inhibitors.

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Small-cell lung cancers (SCLCs) contain near-universal loss-of-function mutations in RB1 and TP53, compromising the G1-S checkpoint and leading to dysregulated E2F activity1. Other cancers similarly disrupt the G1-S checkpoint through loss of CDKN2A or amplification of cyclin D or cyclin E, also resulting in excessive E2F activity2,3. Although E2F activation is essential for cell cycle progression, hyperactivation promotes apoptosis4-9, presenting a therapeutic vulnerability. Cyclin proteins use a conserved hydrophobic patch to bind to substrates bearing short linear RxL motifs10-13. Cyclin A represses E2F through an RxL-dependent interaction10,14, which, when disrupted, hyperactivates E2F15. However, this substrate interface has remained difficult to target. Here we developed cell-permeable, orally bioavailable macrocyclic peptides that inhibit RxL-mediated interactions of cyclins with their substrates. Dual inhibitors of cyclin A and cyclin B RxL motifs (cyclin A/Bi) selectively kill SCLC cells and other cancer cells with high E2F activity. Genetic screens revealed that cyclin A/Bi induces apoptosis through cyclin B- and CDK2-dependent

spindle assembly checkpoint activation. Mechanistically, cyclin A/Bi hyperactivates E2F and cyclin B by blocking cyclin A-E2F and cyclin B-MYT1 RxL interactions. Notably, cyclin A/Bi promoted the formation of neomorphic cyclin B-CDK2 complexes, which drive spindle assembly checkpoint activation and mitotic cell death. Finally, orally administered cyclin A/Bi showed robust anti-tumour activity in chemotherapy-resistant SCLC patient-derived xenografts. These findings reveal gain-of-function mechanisms through which cyclin A/Bi triggers apoptosis and support their development for E2F-driven cancers.

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4. Treatment outcomes for drug-resistant tuberculosis: a retrospective longitudinal Study.

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BACKGROUND: This study examined the treatment outcomes of multidrug-resistant tuberculosis (MDR-TB) in Kazakhstan, where its burden is notably high.
METHODS: The authors conducted a retrospective longitudinal study using the National Tuberculosis Registry, this study analyzed treatment outcomes in MDR-TB patients from 2018 to 2021, and included adult patients (≥ 18 years) who completed a specific treatment. Outcomes were categorized into successful and unsuccessful treatments. Bivariate and multivariate Poisson regression models with modified errors were employed to obtain crude and adjusted risk ratios (aRR).
RESULTS: The study cohort comprised 12,698 cases, of which 10, 306 (81.16%) completed treatment with a successful outcome, while 2,392 (18.84%) had unsuccessful outcomes. Male sex (aRR 1.35, 95% CI 1.24-1.45), urban residency (aRR 1.16, 95% 1.07-1.24), having both extrapulmonary and pulmonary tuberculosis (aRR 1.49, 95% 1.04-2.15), XDR-TB (aRR 1.31, 95% 1.08-1.59), excessive alcohol consumption (aRR 1.43, 95% 1.28-1.59), HIV-positive status (aRR 2.24, 95% 2.01-2.47), and drug abuse (aRR 1.37, 95% 1.10-1.71) significantly elevated the risk of the unsuccessful treatment.
CONCLUSION: Our findings underscore the need for focused strategies to reduce the MDR-TB burden, particularly among adults, male sex, relapsed cases, and XDR-TB. Despite the encouraging findings observed, further studies are necessary to update our estimates.

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5. Treatment outcomes of short-regimen multi-drug resistant tuberculosis in uMkhanyakude district (2018-2022) South Africa: a retrospective, cross-sectional Study.

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BACKGROUND: Rifampicin-resistant / Multidrug-resistant tuberculosis (RR/MDR-TB), remains a major global health challenge, exacerbated by socioeconomic factors, poor treatment outcomes, and rising drug resistance. In response, RR/MDR-TB care has been decentralised to district hospitals in uMkhanyakude Health District to improve treatment access. This study aimed to assess treatment outcomes of patients receiving the nine-month short regimen for RR/MDR-TB in uMkhanyakude District from 2018 to 2022, and to identify socio-demographic and clinical factors associated with treatment success or failure.
METHODS: A retrospective cross-sectional study was conducted among patients aged 18 years and older who received a nine-month short-course RR/MDR-TB treatment regimen at decentralised facilities in KwaZulu-Natal's uMkhanyakude District from 2018 to 2022. Data were collected through clinical chart reviews, and descriptive statistics and multivariable regression analysis were used to identify predictors of treatment outcome.
RESULTS: Among 375 RR/MDR-TB patients on nine-month short-course therapy, 50.1% (n = 188) were Males. Most patients 39.5%, (n = 148) were aged 35-51 years. The treatment success rate was 81.3% (n = 305), with 48.8% (n = 183) cured and 32.5% (n = 122) completing treatment without a confirmed bacteriological cure. Unsuccessful treatment outcomes occurred in 18.7% (n = 70) of patients, including deaths 3.2% (n = 12), treatment failures 3.7% (n = 14), loss to follow-up was 6.7% (n = 25) and treatment interruption leading to unsuccessful outcomes in 5.1% (n = 19). Occupational status, treatment interruption, and adverse drug reactions (ADRs) were significant predictors of treatment failure. Employed patients had higher odds of failure (aOR = 10.5, p = 0.001). Shorter treatment interruption (1 month) was protective (OR = 0.02, p = 0.001). ADRs increased the risk of failure (OR = 4.2, p = 0.001).
CONCLUSION: The treatment success rate for patients on the RR/MDR-TB nine-month

short-course in uMkhanyakude District was high. Being employed was identified as a significant predictor of treatment failure, emphasising the need for targeted interventions for employed individuals. Further research is needed to explore Directly Observed Treatment (DOT) options for employed patients.

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6. Time trend prediction of multidrug-resistant/rifampicin-resistant tuberculosis in treatment initiation centers of North East Ethiopia (2015-2023).

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BACKGROUND: Multidrug-resistant and rifampicin-resistant tuberculosis (MDR/RR-TB) represents a major public health threat and a significant obstacle to global TB control. Analysing trends and forecasting future patterns is

critical for effective resource planning. However, the application of predictive modelling for MDR/RR-TB has not been widely explored in Ethiopia.
OBJECTIVE: This study aimed to analyse the temporal trends and develop a forecasting model for MDR/RR-TB cases recorded at treatment initiation centres in Northeast Ethiopia between 2015 and 2023.
METHODS: A retrospective study of all MDR/RR-TB cases diagnosed from January 2015 to December 2023 in Northeast Ethiopia was conducted using data retrieved from six treatment initiation centers (TIC) registries. Data were collected via Kobo Toolbox and analysed with SPSS v27 for descriptive statistics. Seasonal ARIMA models were developed in R to assess trends and generate forecasts, with model selection based on AIC, BIC, and residual diagnostics. Data quality was ensured through verification and consistency checks.
RESULTS: From an initial 409 identified individuals, 372 were included in the final analysis after excluding transferred cases. Annual case counts demonstrated instability, with a notable rise between 2017 and 2019 (up to 63.6%) and a distinct decline during 2020-2021, followed by a sharp increase in early 2022. A clear seasonal pattern was observed, with case troughs occurring in August and peaks during the dry season (Bega), followed by a decline in December.
CONCLUSION: MDR/RR-TB case trends in Northeast Ethiopia exhibited significant fluctuations over the study period. The pronounced decline in 2020-2021 was likely attributable to service disruptions from the COVID-19 pandemic and regional conflict, while the subsequent surge may reflect a recovery of case detection efforts and the conflict's impact on transmission. TB control programs should prioritize high-risk seasonal periods and ensure resilient systems for timely diagnosis and treatment access amidst external shocks.

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Conflict of interest statement: Declarations. Ethics approval and consent to participate: Ethical clearance was obtained from the Wollo University College of Medicine and Health Sciences Ethical Review Committee (WUERC/322/2025). This study used only secondary, de-identified data from Treatment Initiation Centers and did not involve direct participant contact. Therefore, individual informed consent was waived by the Ethics Committee in accordance with national regulations. Confidentiality was strictly maintained, and the study followed the principles of the Declaration of Helsinki. The findings aim to support public health efforts in managing MDR/RR-TB in the region. Consent for publication: Not applicable. Competing interests: The authors declare no competing interests.

7. Multidrug-resistant tuberculosis household contact screening and management by community healthcare workers in Mongolia: a prospective implementation study.

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BACKGROUND: Mongolia is a high burden country for multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB). The implementation of systematic household TB contact investigation has been very limited despite policy recommendations. We implemented a community-based approach to MDR/RR-TB contact screening and management.
METHODS: We conducted a prospective implementation study in the nine districts of Ulaanbaatar and 10 other provinces. Community health workers (CHWs) were trained to identify and screen household contacts of patients with confirmed pulmonary MDR/RR-TB. Initial screening included symptom assessment for all with chest radiography for adult contacts or tuberculin skin test (TST) for child or young adolescent contacts (<15 years). Follow-up visits to households were conducted quarterly for 12 months. Six months of daily levofloxacin (6Lfx) was offered to eligible contacts, i.e. <15 years, TST-positive and without disease.
FINDINGS: Of 99 people with pulmonary MDR/RR-TB, 349 household contacts were

identified and 347 (99.4%) were screened by CHWs at initial home-based visit. Contact screening coverage remained high (>98%) for each quarterly visit up to 12 months of follow-up. TB was diagnosed in 17 contacts (4.9%); ten from initial screen, seven from follow-up screen and 12 (71%) were children or adolescents. Four contacts were diagnosed with bacteriologically confirmed MDR/RR-TB and two died. 6Lfx was initiated in 15 (43%) of 35 eligible contacts who all completed therapy without interruption.
INTERPRETATION: A decentralized model for the screening and management of MDR/RR-TB contacts implemented by trained CHWs has wider potential for increasing TB detection and prevention in Mongolia and the region.
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8. Geogenomic mapping of drug-resistant Mycobacterium tuberculosis from Ireland and Overseas.

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In this study, we performed an in-depth comparison of genome-sequenced Mycobacterium tuberculosis isolates from Ireland with isolates from other countries. The sequenced isolates from Ireland mostly belonged to Lineage 4 (64.15 %) with Lineages 2 (17.27 %), 1 (13.21 %), 3 (5.22 %), and 5 (0.15 %) also represented. Of these, Lineages 2 (47.57 %) and 4 (34.95 %) accounted for the majority of the isolates that were resistant to at least rifampicin. By performing hierarchical clustering of the genomes, we determined that many drug-resistant (DR) strains of Lineage 2 collected in Ireland belonged to larger international clusters of the bacterium that were dominant in countries that included Estonia, Georgia, Ukraine, and Moldova. Lineage 4 DR-TB strains isolated in Ireland were also commonly part of large international clusters but the major countries differed i.e. Eswatini, Germany, United Kingdom, and Mozambique. Based on single nucleotide polymorphism (SNP) analysis, there was no evidence found of widespread onward transmission of DR-TB isolates in Ireland. This indicates that a key source of DR-TB in Ireland is translocation of M. tuberculosis from countries where specific genetic clusters of drug-resistant strains are prevalent. This study has implications for interpreting future trends in TB drug resistance. As an open economy with extensive international travel connections, Ireland is sensitive to the emergence of resistant isolates of M. tuberculosis elsewhere. In addition to caution being applied with respect to TB presenting in individuals from high multi-drug resistant (MDR) TB burden countries, vigilance is also needed for TB in persons from countries where large phylogenetic clusters of DR-TB occur.

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9. Performance of the low-cost phenotypic thin-layer agar MDR/XDR-TB Colour Test (first generation, 1G, Color Plate Test) for identifying drug-resistant Mycobacterium tuberculosis isolates in a resource-limited setting.

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Update of
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BACKGROUND: The accessible, easy to use and timely, diagnosis of tuberculosis (TB) drug-susceptibility, is often challenging, particularly in resource-constrained settings. We therefore evaluated the phenotypic thin-layer agar based MDR/XDR-TB Colour Test, also known as the "First Generation (1G) Color Plate Test (TB-CX)" performance for detecting resistance of Mycobacterium tuberculosis (Mtb) isolates to selected anti-TB drugs versus other tests routinely used in our setting.
METHODS: A cross-sectional study was conducted on Mtb clinical isolates stored

at the Armauer Hansen Research Institute TB laboratory in Addis Ababa, Ethiopia. Drug-susceptibility testing was performed on 78 Mtb isolates for isoniazid, rifampicin, and moxifloxacin using the Colour Test and the Indirect Proportional Method (IPM) "in house" assay. Isoniazid and rifampicin were also evaluated by the Mycobacterial Growth Indicator Tube (MGIT) commercially available assay. Test accuracy was calculated as % agreement with 95% confidence intervals (95%CI).
RESULTS: The median (range) times in days determining Mtb resistance or susceptibility for the Colour Test, IPM and MGIT assays were of 9 (5-18), 15 (13-18) and 19 (14-21) days, respectively. The Colour Test provided results significantly ($p < 0.001$) more rapidly than the IPM or MGIT assays. The colour test showed a sensitivity and specificity of 91%(95% CI: 87-96) and 87%(95% CI:75-95) for detecting isoniazid resistance,and 93%(95% CI:81-99) and 92%(95% CI:82-97) for detecting rifampicin resistance, respectively, when compared to MGIT DST. For detecting MDR-TB the sensitivity and specificity were 90%(95% CI:76-97) and 96%(95% CI:88-99),respectively. The colour test showed a sensitivity of 97%(95%CI = 87-100) and specificity of 89% (95%CI = 79-96) for detecting isoniazid resistance while for rifampicin resistance,it showed a sensitivity of 82%(95%CI = 64-93)and a specificity of 80%(95% CI = 68-90) rifampicin resistance. Colour Test accuracy compared to IPM to detect isoniazid, rifampicin resistance and MDR-TB was 92% (95%CI = 86-98), 81% (95%CI = 72-90), and 90% (95%CI = 83-96). IPM test accuracy compared to MGIT DST for detecting isoniazid and rifampicin resistance and MDR-TB was 91% (95%CI = 85-97), 83% (95%CI = 75-92), and 85% (95%CI = 77-93), respectively. Moxifloxacin drug-susceptibility testing could not be assessed because only two isolates showed evidence of resistance.
CONCLUSION: The accuracy of Mtb drug-susceptibility testing was similar comparing: Colour Test versus IPM, Colour Test versus MGIT; and comparing IPM versus MGIT. The Colour Test was easy to use and determined drug-susceptibility significantly more rapidly than the IPM and MGIT assays. Thus, implementing the Colour Test in clinical settings could make drug-susceptibility testing more accessible and rapid in high TB burden, and resource-constrained settings, including in Ethiopia.

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Tuberculosis Rehabilitation and Training Center (ALERT) Ethics Review Committee (Protocol number PO-07/23). Waiver of consent to use stored isolates was obtained from the AHRI/All Africa Leprosy and Tuberculosis Rehabilitation and Training Center (ALERT) Ethics Review Committee (Protocol number PO-07/23). Our study adhered to the Declaration of Helsinki. Consent for publication: Not applicable. Competing interests: The authors declare no competing interests.

10. Molecular insights of drug-resistant tuberculosis: genetic mutations and their Profile.

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INTRODUCTION: Drug-resistant tuberculosis (DR-TB) poses a significant public health threat, with molecular diagnostics playing a pivotal role in understanding the genetic mechanisms of resistance. This study focuses on the patterns of genetic mutations observed in DR-TB cases, with the aim to identify key mutations associated with resistance to rifampicin (RIF) and isoniazid (INH).
METHODOLOGY: A total of 6,954 non-duplicate clinical samples were obtained from individuals of all age groups, categorized as TB and DR-TB, from seven linked districts between June 2022 and May 2024. The samples were transported under cold chain conditions to an intermediate reference laboratory. TB was confirmed using fluorescence microscopy, and 1,998 sputum-positive samples were analyzed using line probe assay for characterization of genetic mutations.
RESULTS: Among the analyzed cases, a total of 136 cases of DR-TB were identified. This included 57 cases (41.92%) of multidrug-resistant TB (MDR-TB), 73 cases (53.68%) of INH monoresistance, and 6 cases (4.4%) of RIF monoresistance. The analysis revealed a high prevalence of rpoB MUT3 (S531L) mutations in 52 cases (82.25%), which is associated with RIF resistance. In high-level INH (katG gene mutation) resistance noted in 83 (63.35%) cases, katG MUT1 (S315T1) was predominant, while low-level INH resistance (inhA gene

mutation), inhA MUT1 (C-15T) mutation, was found in 29 (22.13%) cases. Maharajganj and Deoria reported the highest prevalence of rpoB MUT3 (S531L) mutations, while Kushinagar and Sant Kabir Nagar exhibited higher rates of katG MUT1 (S315T1) mutations. Other regions showed notable distribution of rpoB, katG, and inhA gene mutations.
CONCLUSION: The high prevalence of mutations such as rpoB MUT3 (S531L) and katG MUT1 (S315T1) highlights the need for integrating molecular tools into routine workflows to identify genetic mutations. District-specific mutations emphasize the influence of local epidemiological factors on resistance patterns, necessitating region-specific interventions. Continuing research into regional resistance trends are vital to addressing the global DR-TB burden effectively.

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11. What are the Real-Life Dilemmas and Facilitators of Medication Adherence of Patients with Drug-Resistant Tuberculosis: A Qualitative Exploration of Patient Perspectives.

Infect Drug Resist. 2025 Oct 16;18:5351-5364. doi: 10.2147/IDR.S554556. eCollection 2025.

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INTRODUCTION: Drug-resistant tuberculosis (DR-TB) constitutes a global public health crisis, which endangers patients' health, poses a significant transmission risk, and imposes a substantial strain on the healthcare system. Medication adherence is essential for enhancing treatment outcomes and mitigating the proliferation of DR-TB.
PURPOSE: This study aims to explore the real-life dilemmas and facilitators affecting medication adherence in DR-TB patients and provide a reference for improving medication compliance in DR-TB patients.
PATIENTS AND METHODS: A descriptive qualitative study was conducted. 26 patients with DR-TB who were treated with oral medication regimen in a tertiary hospital in Luzhou City, Sichuan Province from March to May 2025 were selected through purposive sampling method for semi-structured interviews, and thematic analysis was used to analyze the data.
RESULTS: Five themes and fourteen sub-themes affecting medication adherence of DR-TB patients were identified, encompassing: Individual physiological traits (age-related variations in the perception of future time, polypharmacy in patients with comorbidities), intricate psychology and behaviors (misconceptions of medication effects, psychological distress resulting from stigma, misunderstanding of disease conditions, downward social comparison, divergences in medicine administration practices), synergy in social networks (multi-dimensional support of family members, support and communication from health providers), differences in family finances and living situations (significant family financial strain, influence of family roles), and constraints on medical insurance services (disparities in health insurance coverage, intricacy of the reimbursement procedure, constraints on reimbursement amounts and coverage).
CONCLUSION: Adherence to medication among DR-TB patients is influenced by intricate factors. Health professionals should intervene on the basis of a comprehensive and dynamic assessment of medication adherence to address these influencing factors at various levels, thereby enhancing adherence and therapeutic outcomes.

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PMID: 41127147

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

12. Association between cardiometabolic risk factors and multidrug-resistant tuberculosis: A case-control study.

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BACKGROUND: Multidrug-resistant tuberculosis (MDR-TB) continues to be a major public health concern, especially in high-burden countries like Nepal. While individual risk factors are known, the cumulative impact of cardiometabolic factors on MDR-TB is not well understood.
METHODS: A health-facility-based, age- and sex-matched 1:2 case-control study was conducted at MDR-TB treatment centers in Gandaki Province, Nepal. MDR-TB patients (cases) and drug-sensitive tuberculosis (DS-TB) patients (controls) were enrolled. Cases were defined as adults (≥18 years) with confirmed MDR-TB; controls were adults with sputum-positive DS-TB. Data on sociodemographics, cardiometabolic risk factors (alcohol, tobacco, abnormal body mass index, hypertension, diabetes), TB literacy, and treatment history were collected using a structured, pretested questionnaire by trained medical officers. Data were analyzed using Stata v13.0. Binary logistic regression was used to assess associations between risk factors and MDR-TB. Ethical approval was obtained from the Nepal Health Research Council and written informed consent was obtained from all participants.
RESULTS: A total of 183 participants (61 cases, 122 controls) were included. Mean age of participants was 42.5 years (SD = 18.5); 73.8% were male. Most participants were from urban areas (74.9%), and 66.7% were unemployed. Cardiometabolic risk factors were present in 79.2% of participants. Alcohol and tobacco use were reported by 59.6% and 45.9%, respectively; 9.8% had diabetes and 7.1% had hypertension. Known TB contact and prior TB history were reported by 26.8% and 31.1% respectively. In multivariate analysis, unemployment (AOR: 5.24, 95% CI: 1.33-20.64), and known TB contact (AOR: 8.89, 95% CI: 2.46-32.15) were significantly associated with MDR-TB. Cardiometabolic risk factors were not significantly associated.
CONCLUSION: Known TB contact and unemployment were significantly associated with MDR-TB, while the cumulative effect of cardiometabolic risk factors showed no

significant impact, indicating that interventions should prioritize established TB-related risk factors.

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13.Patritumab deruxtecan in HR(+)HER2(-) advanced breast cancer: a phase 2 trial.

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Antibody-drug conjugates have shown impressive clinical outcomes, particularly in metastatic breast cancer, but biomarkers to predict response and resistance remain unidentified. Here we report the results of ICARUS-BREAST01, a phase 2 study evaluating efficacy, safety and biomarkers of response and resistance to patritumab deruxtecan (HER3-DXd), in patients with HR+HER2- metastatic breast cancer, who previously progressed on CDK4/6 inhibitors and one line of chemotherapy. From May 2021 to June 2023, 99 patients were enrolled to receive HER3-DXd 5.6 mg kg-1 intravenously every 3 weeks. The study met its primary endpoint, showing an overall response rate of 53.5% (90% confidence interval [44.8-62.1%]). The most frequent adverse events were fatigue (83%), nausea (75%), diarrhea (53%) and alopecia (40%). Exploratory biomarker analysis of baseline tumor samples suggested preliminary associations between overall

response rate and both HER3 spatial distribution and absence of estrogen receptor 1 (ESR1) mutations, as well as between progression-free survival and HER3 expression, pending further validation. Analysis of on-treatment tumor samples showed that treatment efficacy seems to be associated with antibody-drug conjugate intratumoral distribution and interferon response. Overall, HER3-DXd showed promising activity and manageable tolerability in patients with HR+HER2- metastatic breast cancer who progressed on CDK4/6 inhibitors. These findings highlight the need for larger trials to define HER3-DXd efficacy relative to other drugs, including antibody-drug conjugates (ClinicalTrials.gov Identifier: NCT04965766).

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Roche, AstraZeneca, Daiichi Sankyo, Pfizer, Novartis and Eli Lilly. The remaining authors declare no competing interests.

14. Analysis of clinical and bronchoscopic features of multidrug-resistant tracheobronchial tuberculosis.

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OBJECTIVE: Investigate patients' clinical characteristics and bronchoscopic features with multidrug-resistant tracheobronchial tuberculosis.
METHODS: A total of 118 patients with confirmed diagnosis of multidrug-resistant tracheobronchial tuberculosis were selected retrospectively, and the demographic data, clinical characteristics, and bronchoscopic manifestations were analyzed.
RESULTS: Among patients with multidrug-resistant tracheobronchial tuberculosis, the main clinical features were cough (92.3%,109/118) and sputum (83.0%,98/118). The primary infection sites of multidrug-resistant tuberculosis were the right upper bronchus (39.8%,47/118) and the left upper bronchus (37.3%,44/118). The main types of multidrug-resistant tracheobronchial tuberculosis lesions were inflammatory infiltration type (46.6%,55/118) and necrosis type (32.2%,38/118).
CONCLUSION: The clinical manifestations of multidrug-resistant tracheobronchial tuberculosis are non-specific. The main clinical features are cough and fever. It often invades the right upper bronchus. The main bronchoscopic manifestation is inflammatory infiltration.

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15. Impact of fluoroquinolone resistance on the cost-effectiveness of empiric treatment for multidrug- or rifampicin-resistant tuberculosis.

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The WHO recommends the bedaquiline, pretomanid, and linezolid (BPaL) regimen with the additional fluoroquinolone antibiotic moxifloxacin (BPaLM) for initial treatment of multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB). However, fluoroquinolone drug susceptibility testing (DST) coverage for MDR/RR-TB is only around 55% globally, and the efficacy of moxifloxacin may be compromised in settings with high fluoroquinolone resistance. We extended a previous Markov cohort model to assess the cost-effectiveness of the empirical use of BPaLM as a replacement for BPaL for the treatment of MDR/RR-TB in four high MDR/RR-TB burden countries. We obtained fluoroquinolone resistance rates in these countries from WHO surveillance data and parameterised treatment efficacy from recent trial results. We performed scenario analyses across varying

fluoroquinolone resistance prevalence and performed Monte Carlo simulations to generate uncertainty intervals for our primary cost-effectiveness estimates. BPaLM incurred higher costs than BPaL but averted more disability-adjusted life years, with incremental cost-effectiveness ratios below 50% of each country's 2019 GDP per capita. This finding remained robust across a feasible fluoroquinolone resistance prevalence range (0-70%). In the absence of fluoroquinolone DST, empirical use of BPaLM resulted in $58 (interquartile range: $49-$73), $32 (IQR: $23-$53), $35 (IQR: $28 - $51), $174 (IQR: $161 - $209) per DALY averted in Georgia, India, the Philippines, and South Africa respectively. Our findings support the empirical use of BPaLM as a potential replacement for BPaL for the treatment of MDR/RR-TB in the absence of fluoroquinolone DST, even if fluoroquinolone resistance prevalence were to increase, reinforcing recent WHO recommendations.

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16. Scutellarin suppresses Mycobacterium tuberculosis-induced pyroptosis in macrophages by inhibiting the HIF-1α-mediated Warburg effect.

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BACKGROUND: Mycobacterium tuberculosis (Mtb), the causative agent of tuberculosis (TB), remains a major global health threat due to prolonged treatment and drug-resistant strains. Host-directed therapy (HDT), which modulates host-pathogen interactions, offers potential to shorten treatment and limit resistance. This study investigates the effects of Scutellarin (SCU), a flavonoid from Scutellaria baicalensis, on Mtb-infected macrophages within the HDT framework.
METHODS: Anti-pyroptotic and anti-inflammatory effects of SCU were assessed in Mtb-infected THP-1 and J774A.1 macrophages, and in a lipopolysaccharide (LPS)-induced acute lung injury (ALI) mouse model. Mitochondrial function was evaluated by oxygen consumption rate(OCR), membrane potential, and superoxide levels; glycolytic activity was measured by proton efflux rate (GlycoPER). Expression of inflammasome-related markers was analyzed by Western blot, qPCR, ELISA, immunofluorescence, and flow cytometry. The role of hypoxia-inducible factor 1-alpha (HIF-1α) was examined via siRNA knockdown.
RESULTS: SCU inhibited NLRP3 inflammasome activation, reduced IL-1β and IL-18 secretion, and attenuating pyroptosis. It restored mitochondrial integrity by regulating p-DRP1, MFN2, and Cytochrome C expression, and suppressed HIF-1α-mediated glycolytic reprogramming. Silencing of HIF-1α confirmed its role in SCU's mechanism. In vivo, SCU reduced pulmonary inflammation and cytokine release in LPS-induced ALI.
CONCLUSION: SCU alleviates Mtb-induced pyroptosis and inflammation in macrophages by inhibiting the HIF-1α-mediated Warburg effect.

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17. Tanshinones target drug-resistant tuberculosis: efficacy, selectivity, and potential mechanism of action.

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This study evaluates the antimycobacterial potential of tanshinone I (TI), tanshinone IIA (TIIA), and cryptotanshinone (CPT), natural compounds isolated from Salvia miltiorrhiza, against Mycobacterium tuberculosis, the primary etiological agent of tuberculosis. Given the global challenge posed by antimicrobial resistance and the complexity of current treatment regimens, we aimed to identify effective and safe alternative therapies. The compounds' in vitro activity was initially assessed via minimum inhibitory concentration (MIC90) and cytotoxicity index (CI50) determinations, yielding MIC90 values of 1.03, 0.38, and 1.21 μg mL-1 for TI, TIIA, and CPT, respectively, with low toxicity and high selectivity indices. A narrow antimicrobial spectrum was observed upon testing against representative bacteria, fungi, and non-tuberculous mycobacteria (NTM). Combination assays with rifampicin revealed synergism for TI and indifference for TIIA and CPT, as determined by the fractional inhibitory concentration index (FICI). Scanning electron microscopy (SEM) revealed morphological alterations in the bacilli's cell wall, suggesting it as a possible target of the compounds' mechanism of action. Whole genome sequencing (WGS) of resistant strains identified mutations predominantly in PE_PGRS family genes, supporting the hypothesis that tanshinones modulate cell wall structure. Finally, efficacy was confirmed against multidrug-resistant clinical isolates, with MIC90 values near 1 μg mL-1. These findings position TI, TIIA, and CPT as promising candidates for developing new therapies against drug-resistant tuberculosis.

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18. 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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19. Association of vitamin D receptor mRNA expression, vitamin D deficiency and genetic variant in patients with multi-drug resistant pulmonary tuberculosis.

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BACKGROUND: Multi-drug resistant pulmonary tuberculosis (MDR-TB), is a serious threat to world health. Serum levels of vitamin D, a ligand for the VDR that controls VDR mRNA expression, are still poorly understood in MDR-TB.
OBJECTIVE: To study the association of mRNA expression with low vitamin D levels and VDR polymorphisms in patients with MDR-TB compared to normal controls.
METHODS: Study groups consisted of sputum smears and culture-positive MDR-TB at two hospitals in New Delhi, and normal controls were enrolled from a North Indian population. A total 100 (50 MDR-TB subjects and 50 controls) were consecutively enrolled. VDR mRNA expression in peripheral blood mononuclear cells (PBMC) was analysed by Real-time PCR. Serum 25-hydroxyvitamin D, intact parathyroid hormone (iPTH), and calcium (ionized and total) levels were measured, and the correlation between variables was determined. The association between VDR genotype and VDR mRNA expression was studied between MDR-TB and normal controls together with the genotypic and allelic frequencies of the FokI, BsmI, and TaqI VDR polymorphisms were also assessed in between the two groups.
RESULTS: To investigate the role of VDR gene expression and FokI polymorphism in MDR-TB, a total of 100 patients were split into two groups. VDR mRNA expression significantly decreased in MDR-TB patients, being 0.6 times lower than in healthy controls. Notably, the ff genotype was associated with reduced VDR expression, indicating a functional impact on gene regulation. However, there was no appreciable variation in the groups' distribution of FokI alleles and genotypes. These findings highlight the importance of merging genetic and expression data, showing that while the ff variation influences individual expression, it does not distinguish MDR-TB patients from controls.
CONCLUSION: In present study, the VDR gene's FokI polymorphism affects the

levels of VDR mRNA expression, with the ff genotype linked to lower expression in both MDR-TB patients and healthy individuals. Nonetheless, there were no appreciable differences in the genotypic and allelic frequencies of FokI between the groups. These findings suggest that the location of the FokI variation in the population may not be as important to MDR-TB susceptibility as its functional impact on gene expression.

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20. Delamanid-containing regimens over 24 weeks for the treatment of multidrug-resistant/rifampicin-resistant tuberculosis: preliminary results from a single center in a multicenter, prospective, observational study.

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BACKGROUND: Single center preliminary results from a multicenter, prospective, observational study whose aims were to investigate the efficacy and safety of 24-week delamanid-containing regimens in Chinese multidrug-resistant/rifampicin-resistant tuberculosis (MDR/RR-TB) patients.
METHODS: The study included adult patients (≤65 years old) with laboratory-confirmed MDR/RR-TB who were assigned to receive 24 weeks of delamanid (100 mg, twice daily) plus an optimized background regimen (OBR), followed by 5 ~ 12 months of continuation treatment with OBR alone according to

World Health Organization and Chinese guidelines.
RESULTS: Thirty-three patients were enrolled, 26 of whom completed the entire treatment course (intensive + continuation phases), with a treatment success rate of 78.8% (95% CI, 61.1, 91.0). Among the 29 patients who were baseline culture-positive, sputum culture conversion was observed in 25 (86.2%) patients within 24 weeks of delamanid treatment, with a median time to sputum culture conversion of 38 days (interquartile range: 24-77). A total of 18 (54.6%) patients experienced treatment-emergent adverse events (TEAEs), most of them being grade 1 or 2 in severity. Six (18.2%) patients had delamanid-related TEAEs, of whom 5 (15.2%) discontinued the delamanid treatment due to QT interval prolongation (2, 6.1%), gastrointestinal reactions (2, 6.1%) or atrial premature beat (1, 3.0%).
CONCLUSION: The preliminary findings of the present single-center study indicated that the 24-week delamanid-containing regimen demonstrated a promising treatment outcome in Chinese MDR/RR-TB patients. A 24-week follow-up period of safety outcomes was basically consistent with the overall results of the multicenter investigation, and close monitoring of QT interval prolongation should in particular be carried out when delamanid is combined with clofazimine and levofloxacin.
CLINICAL TRIAL REGISTRATION: https://clinicaltrials.gov/study/NCT04421495, identifier NCT04421495.

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PMID: 41090140

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.

21. Innowave MTB/RIF/INH facilitates timely and accurate diagnosis of multiple-drug resistant tuberculosis as a near POCT technique: a multicenter prospective on-site performance evaluation study.

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BACKGROUND: Many rifampicin (RIF)-resistant (RR) tuberculosis (TB) patients remain sensitive to isoniazid (INH), which challenges the strategy of using RR as an instant indicator of multiple-drug resistance tuberculosis (MDR-TB). A molecular test capable of concurrently detecting RIF and INH resistance is urgently needed.
METHODS: The performance of a novel rapid molecular test, Innowave MTB/RIF/INH (InnowaveDX) was evaluated prospectively in three tertiary hospitals. Its capability of detecting resistance to RIF and INH was assessed.
RESULTS: In 767 pulmonary tuberculosis (PTB) patients, InnowaveDX showed significantly higher sensitivity than the Xpert MTB/RIF assay (Cepheid, USA) (74.97% versus 68.18%; $p = 0.003$, $\chi2 = 8.664$). This difference was particularly notable in culture-negative PTB cases (52.73% versus 41.29%; $p = 0.001$, $\chi2 = 10.565$). Both tests demonstrated high specificity in 286 non-TB patients. The overall consistency in RIF susceptibility prediction between InnowaveDX and the Xpert assay was 97.3% (505/519). InnowaveDX identified 83.05% (98/118) of INH-resistant cases as predicted by phenotypic drug susceptibility testing (pDST) and 95.45% (105/110) by another molecular method (MeltPro, Zeesan, China) for INH resistance detection on isolates. In addition, InnowaveDX showed a 99.35% consistency (154/155) with katG, inhA, and ahpC sequencing on sputum samples. The consistency rate for MDR-TB prediction between InnowaveDX and pDST was 93.25% (332/356). The accuracy of using RR to predict MDR-TB varied between 64.1 and 80.5%, depending on the reference method.
CONCLUSION: InnowaveDX is an easy, rapid, and sensitive molecular test for PTB diagnosis that can detect INH and RIF resistance within 3 h, facilitating MDR-TB diagnosis on the first day of hospital admission.

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22. Global trajectory and spatiotemporal epidemiological landscape of multidrug-resistant tuberculosis of spanning 46 years (1990-2035): implications for achieving global end TB goals.

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BACKGROUND: Although MDR-TB is recognized as a significant threat, systematic descriptions of its long-term (>30 years) global spatiotemporal evolution patterns are still limited.
OBJECTIVES: This study conducted a 46-year spatiotemporal analysis of global MDR-TB (1990-2035) to provide key evidence for evaluating and refining the WHO End TB Strategy.
METHODS: We used Global Burden of Disease data to identify identified temporal inflection points in ASIR, ASDR, and DALYs using Joinpoint regression. Spatial clustering was quantified using Moran's I and Getis-Ord hotspot analysis. A Bayesian age-period-cohort model projected MDR-TB incidence from 2022 to 2035.
RESULTS: The male-to-female ratio was approximately 1.5:1. Incidence was highest at 30-60 years, deaths at 60+, DALYs peak at 45-60; children under 14 years of

age significantly affected. ASIR rose from 0.97/100 k (1990) to 6.39/100 k (2000), then declined (APC: -3.15%) post-2005 to 5.62/100 k (2021); males exhibited a sharper increase (+2.39%) and slower decline (-0.71%). ASDR peaked at 2.12/100 k (2002; males 27% higher). DALYs peaked at 89.05/100 k (2003). Sub-Saharan Africa is hyperendemic (Moran's I = 12.38, $p < 0.001$; Somalia: 57.25/100 k), with high-high clusters in Africa/Kyrgyzstan. Projections: Global ASIR declines modestly (-1.62% by 2035), but 480,000 cases expected due to population growth; female incidence drops 7.27% (2025+), male trends stable. CONCLUSION: MDR-TB has proven more challenging than anticipated, with persistent hotspots in sub-Saharan Africa and a disproportionate impact on males, the older adults, and children. Despite a marginal decline in ASIR to 5.46 per 100,000, the absolute number of cases is projected to rise to 480,000 by 2035 due to sustained population growth and aging. This will seriously hinder the WHO End TB Strategy. Addressing MDR-TB should prioritize key populations and regions, targeted resources, tailored interventions, sustained investment in diagnostics and treatment, and stronger government support for patient care.

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23. Divergent Evolution of Malignant Subclones Maintains a Balance between Induced Aggressiveness and Intrinsic Drug Resistance in T-cell Cancer.

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Evolution and outgrowth of drug-resistant cancer cells are common causes of treatment failure. Patients with leukemic cutaneous T-cell lymphoma have a poor prognosis because of the development of drug resistance and severe bacterial infections. In this study, we show that most patients with leukemic cutaneous T-cell lymphoma harbor multiple genetically distinct subclones that express an identical clonal antigen receptor but display distinct phenotypes and functional properties. These coexisting malignant subclones exhibit differences in tissue homing, metabolism, and cytokine expression and respond differently to extrinsic factors like Staphylococcus aureus and cancer drugs. Indeed, although S. aureus toxins selectively enhance activation and proliferation of certain subclones, these responsive subclones are also the most intrinsically sensitive to cancer drugs when the stimuli are removed. Consequently, although the divergent evolution of malignant subclones drives aggressiveness, adaptability, and drug resistance by removing extrinsic stimuli and mapping malignant subclones, we can expose inherent vulnerabilities that can be exploited in the treatment of these cancers.
SIGNIFICANCE: Cancer cells have inherent disparity in hallmark traits, such as aggressiveness and intrinsic drug resistance. We show that segregation of hallmark traits on different coexisting subclones is common and augments adaptability, aggressiveness, and drug resistance of the overall cancer population. Importantly, this segregation exposes vulnerabilities that can be exploited in individualized therapies.

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24. Distribution of Mycobacterium Tuberculosis Lineages and Sublineages by Drug Profile in Ethiopia: A Systematic Review and Meta-Analysis.

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BACKGROUND: Mycobacterium tuberculosis lineages exhibit variability in geographic distribution, transmissibility, and disease phenotype. Ethiopia is one of the countries with the highest prevalence of tuberculosis. The aim of this study was to summarize the proportion of lineages and sublineages by drug resistance profile and TB type.
METHODS: The results were reported in accordance with the PRISMA guidelines. The study protocol was registered with ID CRD42024498336. Studies reporting Mtb lineages and sublineages with drug resistance profiles published between March 2010 and June 2024 were included. I^2 was used to evaluate heterogeneity. A

p-value less than 0.05 and an I^2 value greater than 75% indicated significant heterogeneity.
RESULTS: A total of 5554 Mycobacterium tuberculosis strains were included from 32 studies. The percentage of East African Indian was 26.8% (95% CI: 22.6-30.6), and Euro-American was 64.1% (95% CI: 59.6-68.4) among all TB cases. In studies that included only multidrug- or rifampicin-resistant cases, the percentage of East African Indian was 33.78% (95% CI: 27.81-39.74), while Euro-American was 52.96% (95% CI: 41.32-64.61). Euro-American, followed by East African-Indian, was the predominant lineage across locations and TB types; however, East African-Indian was significantly higher in the Amhara region for both pulmonary TB and extra-pulmonary TB (EPTB) than in Addis Ababa. As defined by spoligotyping, T3ETH (28.22%), CAS1-Kili (18.13%), and T1 (11.54%) were the three most common sublineages among MDR/RR TB cases, while CAS1-Delhi (20.23%), T1 (16.71%), and T3ETH (13.50%) were the most common among susceptible cases.
CONCLUSION: The three most prevalent Mtb sublineages significantly contribute to the TB and drug resistance epidemic; such data are vital for prioritizing contact tracing. The variation in EAI percentage among EPTB cases across regions likely reflects the influence of genetic variation on the prevalence of EPTB. This suggests a need for genomic surveillance to inform the development of more targeted interventions.

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

25. Evaluation of cycloserine dose regimens in an Indian cohort with multidrug-resistant tuberculosis: a population pharmacokinetic analysis.

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Cycloserine is recommended for inclusion in regimens for multidrug-resistant tuberculosis (MDR-TB). Its efficacy is time dependent and relies on the concentration remaining above the minimum inhibitory concentration (MIC); however, there is a concentration-dependent risk of neurotoxicity. Limited pharmacokinetic (PK) data are available in individuals of Indian origin, despite the high burden of MDR-TB in India. We enrolled adults and adolescents receiving cycloserine for MDR-TB at a tertiary hospital in Mumbai, India, in a prospective cohort. Total daily doses ranged from 500 to 750 mg, and participants underwent serial PK sampling on multiple visits starting 1 month after treatment initiation. PK data were analyzed using non-linear mixed-effect modeling. A total of 180 participants (117 females) were enrolled, with a median age of 27 years (interquartile range [IQR] 21-35), weight of 56.0 kg (IQR 46.0-65.9), and fat-free mass of 38.6 kg (IQR 32.3-47.1). Cycloserine PK was best described by a one-compartment model with first-order elimination and transit compartment absorption. Allometric scaling by fat-free mass provided the best adjusment for body size. Serum creatinine improved the model fit and allowed separate estimation of renal and non-renal clearances, whose typical values were 0.589 and 0.901 L/h, respectively. Simulations showed median exposure of 308 mg·h/L after 250 mg twice daily (BID), which is lower than reported in literature. Monte Carlo simulations suggested that doses of 500 or 750 mg BID are required to reach efficacy targets of ≥30% and ≥64% time within dose interval above MIC. The reasons behind the low exposure identified in this Indian population require further investigation.

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

26.Chest CT findings in drug-resistant pulmonary tuberculosis: a comparative analysis of elderly and non-elderly patients.

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BACKGROUND: Drug-resistant pulmonary tuberculosis (DR-TB) remains a critical public health challenge, particularly affecting vulnerable populations such as the elderly, who exhibit higher morbidity and mortality rates. This study aims to elucidate the chest CT characteristics of DR-TB in elderly patients to improve diagnostic accuracy and guide individualized treatment strategies.
METHODS: A retrospective analysis of 183 confirmed DR-TB cases (Huai'an Infectious Disease Hospital, June 2013-June 2023) compared chest CT findings (lesion distribution, extent, and morphology) between elderly patients (≥ 60 years) and non-elderly patients (14-59 years).
RESULTS: Key findings reveal that elderly patients demonstrate a higher frequency of extensive lung involvement, with 76% exhibiting lesions in all lung lobes compared to 40.74% in the non-elderly group ($P < 0.001$). Additionally, the elderly group displayed significantly more pathological features, such as segmental and lobar shadows (61.33% vs. 45.37%, $P = 0.033$) and lung destruction (22.67% vs. 11.11%, $P = 0.035$).
CONCLUSION: The identification of risk factors on chest CT, including the presence of pulmonary and bronchial lesions, highlights the necessity for tailored screening and management strategies for elderly DR-TB patients.

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PMID: 41107823 [Indexed for MEDLINE]

Conflict of interest statement: Declarations. Ethics approval and consent to participate: This study was approved by the Ethics Committee of Huai'an Infectious Disease Hospital (Approval No. HASY2023004) and was conducted in accordance with the Declaration of Helsinki. The requirement for informed consent was waived by the Ethics Committee due to the retrospective design and anonymized analysis of pre-existing imaging data. Consent for publication: Not applicable. Competing interests: The authors declare no competing interests.

27.Immunotherapy for tuberculosis: current strategies and future directions.

Mil Med Res. 2025 Oct 20;12(1):68. doi: 10.1186/s40779-025-00655-7.

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The worldwide dissemination of drug-resistant tuberculosis (TB) presents significant obstacles to conventional anti-TB treatment and prevention methods based on bactericidal antimicrobial drugs, greatly impeding advancements in

combating this most lethal disease. With growing insights into the immunopathogenesis of TB, we are increasingly recognizing the potential of immunotherapeutic strategies aimed at targeting the host. After invading the host, Mycobacterium tuberculosis (M. tuberculosis) induces host cell exhaustion through its own molecules, such as early secretory antigen target-6 (ESAT-6) and di-O-acyl-trehalose, manifested as suppressed proliferative capacity, cytokine production, and cytotoxicity, thereby triggering the onset of TB. In response to this pathogenic mechanism, immunotherapeutic strategies, including cell therapy and immune checkpoint inhibitors, have been developed to promote cytokine production, activate immune cells to exhibit anti-TB activities such as autophagy, and restore immune homeostasis, including the balance between T helper 1 (Th1) and Th2 responses. These approaches have shown promise in restoring host immunity and demonstrating therapeutic effects against TB. However, a comprehensive evaluation of factors such as drug safety, optimal treatment duration, and others, is essential before these strategies can be integrated into routine clinical TB management. The advancement of immunotherapy has the potential to revolutionize current TB management and provide further benefits to patients. This review aims to comprehensively explore the advancements in diverse TB immunotherapeutic strategies, including efficacy, safety, and administration methods, and to explore the challenges and prospects of TB immunotherapy.

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28. Characteristics of compensatory mutations in rifampicin-resistant tuberculosis and their association with compensated transmission in Ningbo, China.
BMC Microbiol. 2025 Oct 6;25(1):634. doi: 10.1186/s12866-025-04390-w.

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BACKGROUND: The global spread of rifampicin-resistant tuberculosis (RR-TB) presents a significant challenge to tuberculosis control, with compensatory mutations hypothesized to offset the fitness cost of drug resistance, thereby facilitating transmission. However, the characteristics and epidemiological impact of these mutations in coastal regions of Eastern China remain inadequately understood. This study aimed to characterize the spectrum of compensatory mutations in RR-TB isolates and to assess their association with transmission dynamics in a well-developed coastal region of Eastern China.
METHODS: We collected RR-TB cases identified through drug-resistance surveillance in Ningbo, China, from 2021 to 2024. Whole-genome sequencing (WGS) was performed on 180 RR-TB isolates to identify resistance-conferring and compensatory mutations, particularly in the rpoA, rpoB, and rpoC genes. Transmission clusters were inferred using single nucleotide polymorphism (SNP) analysis, and the association between compensatory mutations and the risk of RR-TB clustering was evaluated using logistic regression.
RESULTS: Among the 180 RR-TB isolates analyzed, 28.9% harbored putative compensatory mutations, predominantly in rpoC. Isolates with compensatory mutations were significantly more likely to be part of genomic transmission clusters than those without such mutations (odds ratio: 4.28, 95% CI: 2.07-8.85). No significant differences in demographic or clinical characteristics were observed between clustered and non-clustered cases. Phylogenetic analysis indicated ongoing local transmission of compensated RR-TB strains.
CONCLUSION: Compensatory mutations are prevalent among RR-TB strains in coastal Eastern China and are strongly associated with increased transmission, underscoring their role in sustaining the RR-TB epidemic in this region. Enhanced molecular surveillance and targeted interventions are warranted to curb the spread of compensated RR-TB.

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PMID: 41053587 [Indexed for MEDLINE]

Conflict of interest statement: Declarations. Ethics approval and consent to participate: This study was conducted in accordance with the principles of the Declaration of Helsinki. The protocol was approved by the Ethics Committee of

the Ningbo Municipal Center for Disease Control and Prevention. All eligible participants who agreed to participate in the program and signed an informed consent form were required to complete a questionnaire (Table S4) and provide at least one sputum specimen for subsequent studies. Consent for publication: Not applicable. Competing interests: The authors declare no competing interests.

29. Comprehensive analysis of mutations associated with rifampicin- and isoniazid-resistant tuberculosis in a high-burden setting.

Rev Soc Bras Med Trop. 2025 Sep 22;58:e01842025. doi: 10.1590/0037-8682-0184-2025. eCollection 2025.

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BACKGROUND: In this study, we aimed to describe the mutations associated with first-line drug resistance in Mycobacterium tuberculosis complex (MTBC) isolates from São Paulo, Brazil, between 2019 and 2021.
METHODS: Mutations in the coding regions of rpoB and katG genes and in the promoter region of the inhA gene in MTBC clinical isolates were detected using the GenoType MTBDRplus assay (LPA). All mutations inferred by LPA were sequenced.
RESULTS: Of the 13,489 MTBC isolates with valid LPA results, 657 (4.9%) harbored mutations. The overall prevalence rates of rifampicin-resistant (RIF-R) tuberculosis (TB), isoniazid-resistant (INH-R) TB, and multidrug-resistant (MDR) TB were 1.5, 2.0, and 1.2%, respectively. A significant proportion of RIF-R isolates presented inferred rpoB mutations (89.1%), most of which were the borderline H445N mutation. The inhA promoter C-15T mutation was predominant among the INH-R isolates (52.8%). Most MDR isolates presented rpoB S450L + katG S315T1 mutations. Gene sequencing identified mutations not included in the catalogue of mutations published by the World Health Organization. Phenotypic drug susceptibility testing on isolates with inferred rpoB mutations revealed that the 0.5 µg/mL critical concentration of RIF failed to detect most borderline mutations when using the BACTEC MGIT 960 system.
CONCLUSIONS: These findings emphasize the need for continuous surveillance and the integration of molecular and phenotypic methods to ensure an accurate detection and management of drug-resistant TB in high-burden settings.

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30.Low-level BTZ-043 resistance in Mycobacterium tuberculosis and cross-resistance to bedaquiline and clofazimine.

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BACKGROUND: Multidrug- and extensively drug-resistant strains of Mycobacterium tuberculosis complex (MTBC) remain a significant global health challenge. This study investigates resistance mechanisms to BTZ-043, a novel decaprenylphosphoryl-β-D-ribose 2'-epimerase (DprE1) inhibitor, and its potential cross-resistance with bedaquiline (BDQ) and clofazimine (CFZ).
METHODS: BTZ-043-resistant mutants were generated in M. tuberculosis H37Rv by serial exposure to escalating drug concentrations. Minimum inhibitory concentrations (MICs) for BTZ-043 were determined for 130 wild-type strains, including 60 H37Rv independent cultures and 70 diverse clinical isolates, plus 33 non-wild-type clinical strains with known BDQ susceptibility. MICs were correlated with whole-genome sequencing (WGS) data to identify genetic factors underlying resistance.
RESULTS: The MIC distribution for clinical MTBC strains was similar to the reference strain, with a mode of 0.002 µg/mL. WGS of resistant mutants revealed

mutations in dprE1 and Rv0678. Rv0678 and dprE1 mutations resulted in 4- to 8-fold and >1,000-fold increase in MIC compared with the reference mode, respectively. Sequential clinical strains from BDQ-treated patients showed increased MICs and Rv0678 mutations, indicating low-level cross-resistance. However, Rv0678 mutations in BDQ-susceptible strains did not affect BTZ-043 MICs.
CONCLUSION: Rv0678 mutations confer low-level cross-resistance to BTZ-043, BDQ, and CFZ, with variable effects on susceptibility. These findings highlight the complexity of resistance mechanisms and the need for ongoing surveillance and early resistance assessments in drug development.

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PMID: 41089235

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31. Incidence and predictors of mortality among persons with rifampicin-resistant tuberculosis and HIV in Mozambique.

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Rifampicin-Resistant Tuberculosis (RRTB) is associated with a high risk of mortality during treatment. This study aims to describe the baseline characteristics associated with incidence of mortality in persons with

rifampicin-resistant tuberculosis (P-RRTB) in a rural setting in Mozambique. We analyzed cohort data collected retrospectively from paper medical files and electronic medical records of P-RRTB who were routinely treated at Carmelo Hospital of Chokwe (Gaza province, Mozambique), from 1st January 2015 to 31st December 2020. Kaplan-Meier survival curves and adjusted Cox regression analyses were used to model the time to death and associated factors of mortality. Overall, 151 P-RRTB contributed to a total number of 1812 person-months (PM) of treatment follow-up. The overall mortality rate was 1.9 per 100 person-months (95% confidence interval [CI]: 1.3-2.1). Adjusted Cox regression predicted higher risk of mortality in those treated with injectable anti-RRTB second line drugs (SLD), (adjusted hazard ratio [aHR] 3.72, 95% CI 1.23-11.22, p = 0.020), had a parenchymal lesion with more than 50% fibrosis (aHR 3.06, 95% CI 1.38-6.79, p = 0.006), presented right ventricular dysfunction on the echocardiogram with venous assessment (aHR 3.18, 95% CI 1.15-8.83, p = 0.026), and manifested baseline hemoglobin (Hgb) = 8.0-9.9 g/dL (aHR 2.82, 95% CI 1.09-7.27, p = 0.032), as well Hgb < 7.9 g/dL (aHR 3.06, 95%CI 1.24-7 0.51, p = 0.015). However, lower risk of mortality was predicted in those who had an optimal immunovirological response to ART (aHR 0.18, 95% CI 0.04-0.93, p = 0.040). Kaplan-Meier analysis showed higher cumulative incidence of mortality after 3 months of follow-up, above 26% in those with immunovirological failure to ART therapy (p = 0.006), 45% with Hgb < 7.9 g/dL (p < 0.001), 23% in treated with injectables-based drugs (p = 0.03), 39% with parenchymal lesion > 50% fibrosis on the chest X-ray (p < 0.001), 56% with right ventricular dysfunction (p = 0.003). Mortality risk among P-RRTB was higher in those with anemia, injectable anti-RRTB medications, lung lesions > 50% fibrosis, and right ventricular dysfunction.

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PMID: 41120609 [Indexed for MEDLINE]

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Bioética para a Saúde de Gaza, 19/CIBS-Gaza/2021). All information obtained during the study was kept confidential. Analysis was performed on de-identified aggregated data. Furthermore, this study was conducted in accordance with the principles of the Declaration of Helsinki. Consent for publication: We performed analysis on routine administrative data; consent for publication is not applicable.

32. Global research trends in BPaL and BPaLM regimens for drug-resistant tuberculosis: a bibliometric analysis.

Trop Dis Travel Med Vaccines. 2025 Oct 3;11(1):33. doi: 10.1186/s40794-025-00269-w.

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BACKGROUND: The introduction of BPaL and BPaLM regimens has revolutionized drug-resistant tuberculosis treatment, offering superior efficacy, shorter duration, and better tolerability than conventional therapies. Despite their rapid WHO guideline incorporation, no prior bibliometric analysis has been conducted on this topic. This study addresses this gap by mapping global knowledge production, collaborations, and thematic trends to inform future research and implementation strategies.
METHODS: We analyzed Scopus-indexed publications using controlled vocabulary for BPaL/BPaLM regimens. From 551 initial records, 120 met inclusion criteria after screening. Bibliometrix and VOS Viewer software evaluated publication trends, authorship, institutional/geographical contributions, citations, and keyword networks. Visualization tools mapped collaborations and thematic clusters, while statistical methods assessed growth rates and citation impacts.
RESULTS: The study identified 1,081 authors, with publications growing at 11.61% annually and peaking in 2024 (n = 56). International collaborations featured in 53.33% of studies, led by the US (n = 56), UK (n = 25), and South Africa (n = 20). Johns Hopkins University was the top institution (n = 56), and Antimicrobial Agents and Chemotherapy the leading journal (n = 15). Landmark 2019 publications had the highest citation rate (13.05/year). Thematic analysis revealed categorization into three domains: pathogen and drug resistance,

treatment regimens and efficacy, and demographics and clinical studies. Strong collaborations linked high-income and high-burden countries, notably the US and South Africa.
CONCLUSION: This first bibliometric assessment of BPaL/BPaLM research highlights progress in evidence generation but reveals gaps in implementation science and equitable knowledge production. Future work should address operational challenges, special populations, and resistance monitoring. These insights can guide researchers, policymakers, and funders to optimize TB control programs and advance global elimination goals.

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PMID: 41044664

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33. Determinants of treatment success and cost implications in MDR/RR-TB patients: a prospective cohort study in China.

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Multidrug-resistant or rifampicin-resistant tuberculosis (MDR/RR-TB) remains a critical global health threat. While novel regimens offer promise, the impact of socioeconomic determinants and clinical factors on treatment success is inadequately characterized, hindering targeted interventions. A prospective cohort study was conducted across 13 TB-designated hospitals in Jiangsu Province, China from 2021 to 2022. Binary logistic regression identified predictors of treatment success, with model performance assessed via Receiver Operating Characteristic (ROC) curves assessing predictive performance. The overall treatment success rate for patients with MDR/RR-TB was 67.38%, with the short-term regimen achieving a success rate of 74.4%, new long-term oral regimens at 66.7%, new long-term injectable regimens at 71.0%, traditional long-term regimens at 60.3%, though differences were not statistically significant (P = 0.454). Patients educated at the junior and senior high school levels (OR = 3.95, 95% CI: 1.70, 9.19, P = 0.001) and at the college level or above (OR = 3.13, 95% CI: 1.03, 9.51, P = 0.044) exhibited significantly higher success rates compared to those with primary school education or lower. Moreover, it underscores the irrelevance of cost to treatment outcomes. Additionally, urban workers (OR = 4.53, 95% CI: 1.22, 16.86, P = 0.024), urban residents (OR = 4.61, 95% CI: 1.25, 17.04, P = 0.022), and individuals covered by other medical insurance, including public medical insurance (OR = 8.82, 95% CI: 1.50, 51.76, P = 0.016), demonstrated higher treatment success rates compared to those without medical insurance. Conversely, hypokalemia (OR = 0.12, 95% CI: 0.02, 0.61, P = 0.010) was identified as a risk factor for successful treatment. Treatment costs demonstrated no significant association with outcomes (OR = 1.06, 95%CI: 0.96, 1.17, P = 0.284). Prioritizing health literacy programs, insurance expansion, and hypokalemia monitoring is essential for improving treatment success.

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34. Clinical Outcome of Rifabutin-based Treatment for Pulmonary Tuberculosis in Solid Organ Transplant Recipients.

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BACKGROUNDS: Rifabutin is often used instead of rifampin to treat tuberculosis (TB) in solid organ transplant recipients (SOTRs) due to fewer drug interactions with immunosuppressants. However, data on its efficacy are limited.
METHODS: A retrospective, case-control study was conducted at a tertiary care center in Korea. SOTRs aged ≥18 years with culture-positive pulmonary TB treated with isoniazid and rifabutin for >80% of the treatment duration were included. Those with rifampin-resistant TB or who discontinued immunosuppressants prior to TB diagnosis were excluded. Each SOTR was matched to three non-SOTR controls treated with rifampin-based regimens. The primary outcome was treatment completion without early relapse. Logistic regression with and without overlap weighting was used for analysis.
RESULTS: Forty SOTRs and 120 non-SOTRs were analyzed. Baseline TB severity markers (cavitary lesions, smear/culture-positivity) were comparable, but extrapulmonary TB and isoniazid resistance were more common in SOTRs. Treatment duration was longer in SOTRs (median 272 vs 187 days, P < .001). The primary outcome occurred in 90% of SOTRs and 96.7% of controls (P = .108). Treatment completion was lower in SOTRs (92.5% vs 100%, P = .015). No significant differences were observed in TB recurrence or 1-year mortality. TB-attributable deaths were absent in both groups. After overlap weighting, no significant difference was found in the primary outcome (aOR 0.36; 95% confidence interval, 0.01-10.41). Allograft rejection and failure occurred in 10% and 12.5% of SOTRs, respectively.
CONCLUSIONS: Rifabutin-based therapy in SOTRs achieved treatment outcomes

comparable to rifampin-based regimens in non-SOTRs, supporting its use in this population.

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PMID: 41064696

Conflict of interest statement: Potential conflicts of interest. The authors declare that they have no conflicts of interest.

35. In Vitro Antimicrobial Activity of Contezolid Against Mycobacterium tuberculosis and Absence of Cross-Resistance with Linezolid.

Microorganisms. 2025 Sep 22;13(9):2216. doi: 10.3390/microorganisms13092216.

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Tuberculosis (TB) persists as a formidable global health threat, especially with the rising incidence of multidrug-resistant strains. This study aimed to evaluate the in vitro activity of contezolid, a novel oxazolidinone antibiotic, against Mycobacterium tuberculosis (Mtb) and assess potential cross-resistance with linezolid. Thirty-one Mtb clinical isolates (5 susceptible, 8 multidrug-resistant [MDR], 18 pre-extensively drug-resistant [pre-XDR]) were tested. Minimum inhibitory concentrations (MICs) of contezolid and linezolid were determined, along with mutation resistance frequencies. Intracellular replication inhibition in macrophages and whole-genome sequencing of resistant colonies were assessed. Cytotoxicity was evaluated via luciferase-coupled ATP assay. The MIC50 and MIC90 values of contezolid were comparable to those of

linezolid. Contezolid induced higher mutation frequencies in 7 isolates. At 12 mg/L, both drugs similarly inhibited intracellular Mtb replication. Whole-genome sequencing revealed that the mce3R gene was linked to contezolid resistance, with no cross-resistance observed between two drugs. No significant cytotoxicity was observed in contezolid-treated mouse peritoneal macrophages ($p > 0.05$). Contezolid exhibits anti-Mtb activity, with mce3R potentially associated with resistance. No cross-resistance with linezolid was found.

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36. Machine learning identifies MiRNA biomarkers and immune mechanisms in active Tuberculosis.

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Tuberculosis (TB), caused by Mycobacterium tuberculosis (Mtb), remains a major global public health threat. The rising prevalence of HIV/TB co-infection and multidrug-resistant tuberculosis (MDR-TB) has further intensified this challenge. This study aims to explore the role of microRNAs (miRNAs) in the immune response to Mtb infection and to identify potential miRNA biomarkers for active TB diagnosis using machine learning techniques. miRNA expression profiles were retrieved from the Gene Expression Omnibus (GEO) database (accession number: GSE70425). Differential expression analysis between active TB and latent TB infection (LTBI) patients was conducted using the "limma" package, with a screening threshold of $|logFC| > 0.25$ and p-value < 0.05. Key differentially expressed miRNAs (DE-miRNAs) were further refined using machine learning

algorithms, including least absolute shrinkage and selection operator (LASSO) regression, support vector machine-recursive feature elimination (SVM-RFE), and Boruta. TargetScan was employed to predict miRNA target genes, and a regulatory network was visualized using Cytoscape. Subsequently, Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses were conducted to elucidate the functional roles of target mRNAs. Nine machine learning models were developed based on the selected miRNAs, and their predictive performance was assessed using metrics including AUROC, accuracy, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). In vitro experiments were performed using THP-1 macrophages to establish an Mtb infection model. Cells were transfected with miR-3607-3p mimics and negative controls, followed by flow cytometry for apoptosis detection, Western blot for protein expression analysis, and Quantitative Real-Time PCR (qRT-PCR) for validation of apoptosis-related gene expression. A total of 72 differentially expressed miRNAs were identified. Key miRNAs, including hsa-miR-3607-3p, hsa-miR-148b, and hsa-miR-519e, were identified through multiple machine learning methods, with hsa-miR-3607-3p emerging as the primary candidate miRNA. The nine machine learning models exhibited robust predictive performance in both the training and test sets. PPI network and functional enrichment analyses indicated that the target genes of hsa-miR-3607-3p are primarily associated with cell growth and apoptosis-related pathways. In vitro experiments further suggested that hsa-miR-3607-3p may modulate the apoptotic response of THP-1 cells to Mtb infection via a caspase-dependent mechanism. miR-3607-3p was upregulated in active TB patients and may modulate the apoptosis of THP-1 cells during Mtb infection via a caspase-dependent pathway. The mechanism of this miRNA offers preliminary insights into the immune regulation of tuberculosis. miR-3607-3p may serve as a potential biomarker for the early diagnosis and intervention of active TB; however, its clinical applicability necessitates further validation through larger sample sizes and multicenter studies.

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37. Mycobacterium tuberculosis complex Lineage 1: A neglected cause of tuberculosis.

PLoS Negl Trop Dis. 2025 Oct 9;19(10):e0013513. doi: 10.1371/journal.pntd.0013513. eCollection 2025 Oct.

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The Mycobacterium tuberculosis complex (MTBC) phylogenetic lineages 1-4 (L1-L4) are the main causes of human tuberculosis (TB). Until now, most of the focus in the TB field has been on MTBC L2 and L4, as these two lineages are geographically widespread and have been repeatedly associated with multidrug resistance. By comparison, MTBC L1 has received little attention, partially because of its restricted geographical range that mainly includes low- to middle-income countries in South and Southeast Asia, and East Africa. However, recent estimates indicate that MTBC L1 is in fact the most common cause of human TB in terms of absolute numbers of TB patients, particularly among several high TB burden countries. As more L1 strains are being sampled in L1-endemic countries, the high genetic diversity of this geographically restricted MTBC lineage is slowly uncovered. This discovery has also impacted L1 nomenclature, which has been modified as new distinct L1 clades were identified. In parallel to the genomic discoveries ushered by progress in whole genome sequencing, clinical researchers have also studied several phenotypes that better describe L1 TB disease. L1 strains have been shown to have increased vulnerability to oxidative stress, which was associated with decreased virulence in animal and in vitro models. L1 infection also shows possible association with extrapulmonary TB and asymptomatic TB. However, despite belonging to the same lineage, L1 strains display phenotypic diversity that can be attributed to high within-lineage genetic diversity and possibly the interaction of different L1 genotypes with different human host genotypes. Among the clinical phenotypes that show heterogeneity are bacterial factors, immune profiles, and clinical virulence. The traditional view regarding the reduced transmissibility in L1 is now being challenged by new data indicating that L1 may be as transmissible as L2 or L4. Lastly, although historically referred to as being negatively associated with drug resistance, there is indication that the contribution of L1 to TB drug resistance is significant and that it may evolve drug resistance in ways distinct from those of other MTBC lineages.

original author and source are credited.

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PMCID: PMC12510564
PMID: 41066423 [Indexed for MEDLINE]

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

38.Incorporation of macrophage immune stresses into an intracellular assay of drug tolerance in Mycobacterium tuberculosis.

Antimicrob Agents Chemother. 2025 Oct;69(10):e0079525. doi: 10.1128/aac.00795-25. Epub 2025 Sep 11.

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Update of
bioRxiv. 2025 May 09:2025.05.09.653069. doi: 10.1101/2025.05.09.653069.

Development of new and improved tuberculosis (TB) chemotherapies is hampered by antibiotic resistance and drug tolerance by Mycobacterium tuberculosis (Mtb). Phenotypic drug tolerance, a phenomenon where Mtb populations can temporarily survive therapeutic antibiotic concentrations, represents a significant hurdle to TB treatment and is indeed one of the factors responsible for prolonged TB therapy. Assays that can identify compounds with improved efficacy against drug-tolerant Mtb are urgently required to improve TB treatment regimens. Here, we report the development of a 96-well plate assay capable of identifying anti-Mtb drugs with activity against drug-tolerant Mtb in physiologically relevant intracellular environments within macrophages. Primary murine macrophages, modified either by immunological activation or specific CRISPR/Cas9 gene knockouts to generate tolerance-inducing environments, were infected with an Mtb strain constitutively expressing luciferase. Following drug exposure, differences in bacterial survival were measured by bacterial outgrowth after lysis of the host macrophages. By monitoring Mtb luciferase in infected macrophages before, during, and after drug treatment, we confirmed earlier observations that host immune stresses trigger induction of drug tolerance. However, while host stresses induced tolerance against some anti-TB compounds,

the same host stresses were synergistic with other anti-TB drugs. Our assay provides the ability to profile the activities of anti-TB drugs on bacteria in intracellular host environments, which is critical to the rational design of drug combinations that provide optimal coverage of the Mtb sub-populations in the infected host.

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PMID: 40934365 [Indexed for MEDLINE]

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

39. The acetyltransferase CysE modulates virulence and drug resistance of Mycobacterium tuberculosis by interfering with oxidative stress responses.

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Acetyltransferases play a crucial role in biological processes by modifying a variety of substrates. However, their roles in the virulence of Mycobacterium tuberculosis (M. tb) are poorly understood. To systematically investigate the

roles of acetyltransferases in M. tb, we constructed an acetyltransferase mutant library using CRISPR-assisted genome editing and screened for genes that are essential for mouse infection. Seven acetyltransferases were identified as essential for lung infection of M. tb. cysE, encoding a serine acetyltransferase, was confirmed to be required for virulence of M. tb in mice and its replication in macrophages. Further experiments revealed that mutation of cysE or inhibition of CysE by small molecular chemical increased sensitivity to clofazimine treatment. Finally, we demonstrated that cysE is involved in mitigating oxidative stress, which modulates the virulence and drug resistance of M. tb. Our study suggests that targeting cysE offers potential for the development of anti-tuberculosis drugs, particularly for enhancing treatment regimens for drug-resistant tuberculosis through the synergistic effect with clofazimine.

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40. Improved detection of isoniazid-heteroresistant Mycobacterium tuberculosis subpopulations by droplet digital PCR compared to MeltPro TB assay.

Microbiol Spectr. 2025 Oct 7;13(10):e0003025. doi: 10.1128/spectrum.00030-25. Epub 2025 Aug 26.

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Drug resistance in Mycobacterium tuberculosis (Mtb), especially isoniazid (INH)

resistance, challenges tuberculosis control. This study evaluated droplet digital PCR (ddPCR) against the traditional MeltPro TB assay. A total of 77 INH-resistant samples from Beijing Chest Hospital, China, underwent ddPCR, drug susceptibility testing, and Sanger sequencing. Of the 73 valid samples, MeltPro detected 55 INH-resistant and 18 heteroresistant samples; ddPCR found 55 high-frequency mutations, 11 of the 18 heteroresistant by MeltPro as heteroresistant, and 6 of the 7 below limit as sensitive, 1 as Nocardia. Using ddPCR as a secondary screening tool for MeltPro results can screen false positives in MeltPro, improving INH resistance detection accuracy (98.63% vs. 89.04%). DdPCR technology performs excellently in tuberculosis drug resistance detection and provides strong technical support for the accurate diagnosis and treatment of tuberculosis.
IMPORTANCE: Tuberculosis has emerged as a significant threat to global health, bringing numerous new cases and a large number of deaths annually. Isoniazid (INH), as a first-line treatment drug, plays a crucial role. However, the emergence of its drug resistance poses a tough challenge for tuberculosis control. Currently, the methods for detecting INH resistance and heteroresistance have limitations like the slow speed of traditional culture tests and the insufficient sensitivity of molecular methods. Therefore, improving the diagnostic efficacy of the detection results for INH resistance is crucial for the treatment of tuberculosis.

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PMID: 40856496 [Indexed for MEDLINE]

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

41. Performance evaluation of alternative bacteriological measures of response to MDR/RR-TB therapy during the initial 16 weeks of treatment.

BMC Infect Dis. 2025 Oct 15;25(1):1336. doi: 10.1186/s12879-025-11785-7.

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Update of
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BACKGROUND: Monitoring response to Multi-Drug-Resistant Tuberculosis (MDR-TB) treatment is burdensome to TB programmes and may benefit from alternative effective tools. We evaluated the concordance of alternative bacteriological measures of response to therapy (AMRT) with sputum culture during the initial sixteen weeks of MDR-TB treatment.
METHODS: In a prospective study of MDR/RR-TB among smear positive adults, aged 18-years and above. Pooled early morning and spot sputa were obtained before treatment initiation (95% on Bdq, Lzd, Lfx, Cfz, Cs regimen) and at weeks 2, 4, 6, 8, 12, and 16 during treatment between 14/02/2020 and 09/02/2024. Samples were tested using Concentrated Fluorescent Microscopy (CFM), Fluorescein-di-acetate (FDA)-Acid Fast Bacilli (AFB) vital smear microscopy, the Tuberculosis-Molecular bacterial load assay (TB-MBLA), and Middle brook 7H11 selective (MB7H11S) colony-forming units as the AMRT. Concordance of the AMRT for sputum conversion determination was compared to Mycobacterial Growth Indicator Tube (MGIT) culture conversion at weeks 12 and 16 of treatment.
RESULTS: A total of 101 MDR/RR-TB patients were screened of which 42 were smear negative. Fifty-nine participants were enrolled, of whom 58 (98%) provided baseline sputa and these were included in the analysis. The concordance, n/N (%) of each AMRT test with MGIT culture conversion at week 12 were: 31/35(88.6%) for CFM, 32/33 (97.0%) for FDA, and 25/26 (96.2%) for TB-MBLA, and 11/11 (100%) for MB7H11S. At week 16, concordance of each AMRT were: 39/40 (97.5%) for CFM, 35/36 (97.2%) for FDA, 32/32 (100%) for TB-MBLA, and 15/15 (100%) for MB7H11S. Among people living with HIV, the concordances of AMRT with MGIT culture conversion varied at week 8 but was 100% for all tests at weeks 12 and 16. Baseline clinical and/or bacteriological factors did not influence the concordance of AMRT to MGIT culture conversion at weeks 12, and 16.
CONCLUSION: Our data show that concentrated Fluorescent smear, Fluorescein-di-acetate smear microscopy, and TB-MBLA are suitable alternative

measures of response to TB therapy compared to MGIT culture among MDR-TB participants. Use of these alternative rapid methods may allow timely decision making as well as rapid evaluation of alternative MDR-TB treatment regimens.

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PMCID: PMC12522586
PMID: 41094385 [Indexed for MEDLINE]

Conflict of interest statement: Declarations. Ethics approval and consent to participate: The study was approved by the Makerere University School of Biomedical Sciences Research Ethics committee (SBS-REC #651) and the Uganda National Council for Science and Technology (UNCST #HS471ES). Our study adhered to the Declaration of Helsinki and the national guidelines. Eligible participants gave a written informed consent to participate in the study. Consent for publication: Not applicable. Competing interests: The authors declare no competing interests. Conflict of interest: The authors have declared that no competing interests exist.

42. Correction: Unraveling the Secrets Behind the Multidrug-Resistant Tuberculosis Treatment Outcome in Chronic Renal Failure Patients Requiring Hemodialysis: A Systematic Review.

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PMCID: PMC12462815
PMID: 41020011

Conflict of interest statement: No competing interests declared.

43. Microbiological evidence for the trisubstituted benzimidazoles targeting MmpL3 in Mycobacterium tuberculosis.

Antimicrob Agents Chemother. 2025 Oct;69(10):e0036825. doi: 10.1128/aac.00368-25. Epub 2025 Aug 19.

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New anti-tuberculosis (TB) drugs with novel modes of action are in great demand due to the complex treatment regimens as well as the rising number of multidrug-resistant TB cases. We recently re-evaluated a few 2,5,6-trisubstituted benzimidazole derivatives (SBZ) previously demonstrated to have potent antitubercular activity. These compounds displayed favorable MICs and significantly reduced bacterial counts in an acute mouse infection model. Although this antitubercular lead series was initially reported to inhibit

mycobacterial cell division, our findings suggest that its primary activity likely involves other cellular targets. By using bacterial cytological profiling, we observed that SBZ-treated Mycobacterium tuberculosis cells exhibit cell wall-damaging phenotypes resembling those caused by known cell wall biosynthesis inhibitors, such as AU1235 and SQ109, that mostly target the membrane protein large 3 (MmpL3). Whole-cell assays further supported the findings by showing activation of the iniBAC operon and accumulation of intracellular ATP. The antitubercular activity of SBZs was tested against engineered mycobacterial strains that have the transcriptionally regulated mmpL3 gene expression, confirming that SBZs engage the MmpL3 target in the cell. Strains with mutations in mmpL3 exhibited either low- or high-level resistance to the SBZs. A molecule docking model is proposed, based on a high-resolution crystal structure of MmpL3, which could be useful in reconciling the inhibition mechanism and suggesting a further development of MmpL3 inhibitor starting with the SBZ scaffold.

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PMID: 40827962 [Indexed for MEDLINE]

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

44. Children, caregivers and health workers' perceptions and experiences of the XTEMP-R tool to improve tuberculosis treatment.

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Treating drug-resistant tuberculosis (DR-TB) in children remains a significant challenge for patients, caregivers, and health systems, despite advances in child-friendly drug formulations. While new formulations offer benefits, their widespread availability is limited, and many exhibit poor palatability. A key strategy to improve administration and mask the taste of paediatric TB medications involves creating extemporaneous suspensions. However, this often requires pharmaceutical services not readily available in high-burden settings. To address this, the Global Alliance for TB Drug Development (TB Alliance) developed XTEMP-R, an inexpensive prototype tool designed to facilitate home-based preparation of liquid TB medication suspensions. This study explored the experiences and perceptions of children, their caregivers, and health workers regarding the XTEMP-R tool for preparing extemporaneous DR-TB treatment suspensions. We collected qualitative data from two sites in South Africa. The first component involved interviews with 17 caregivers and 12 health workers, followed by focus group discussions, with participants directly interacting with the XTEMP-R tool. The second component comprised 31 interviews with 11 caregivers of 13 children who used the XTEMP-R tool for home administration. Case descriptions were iteratively refined and analyzed using deductive thematic analysis. Findings indicate that children, caregivers, and health workers found the XTEMP-R tool easy to use, clean, and store, appreciating its appealing color and durability. Home users reported that the tool simplified treatment preparation and administration, reducing time and relational burdens associated with DR-TB treatment. While XTEMP-R effectively addressed usability challenges related to drug preparation, fundamental obstacles concerning medication palatability, nausea, and side effects remain significant barriers. Importantly, the tool appeared to foster increased treatment responsibility among some children, suggesting a potential pathway to improve therapeutic engagement and agency. This research underscores the XTEMP-R tool's potential to ease paediatric DR-TB treatment and highlights crucial areas for design refinement, ultimately aiming to enhance adherence and overall outcomes.

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PMID: 41060999

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

45. Progress of single-cell sequencing technology in immunotherapy for tuberculosis.

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According to the 2024 World Health Organization (WHO)Global Tuberculosis (TB)Report, tuberculosis remains the leading cause of death from a single infectious agent, with 10.8 million new cases and 1.25 million deaths in 2023. Early and standardized treatment upon definitive diagnosis holds significant importance for the prevention and prognosis of pulmonary tuberculosis patients. However, the number of drug-resistant tuberculosis(DR-TB) cases is increasing, while the interventions for tuberculosis are becoming increasingly limited. There is an urgent need to develop new rapid diagnostic methods and effective treatment drugs. Recent advances in tuberculosis immunotherapy have shown promising results. Novel therapeutic vaccines like M72/AS01E demonstrate 54% efficacy in preventing pulmonary TB, while host-directed therapies including nano-based drug delivery systems offer enhanced treatment outcomes. The immune system plays a vital role in the development and regulation of tuberculosis. Single-cell sequencing(SCS) technology enables comprehensive analysis of immune cells at the single-cell level, revealing the functions, states, distributions, and communication behaviors among immune cell subpopulations. These insights contribute to understanding the pathogenesis and discovering new diagnostic markers and therapeutic targets in tuberculosis. This review provides a critical overview of the immunological mechanisms underlying tuberculosis, immunotherapy for tuberculosis, and single-cell sequencing technology, with specific focus on key findings from recent studies and their clinical implications. It primarily focuses on discussing the research progress of single-cell sequencing technology in the context of tuberculosis immunotherapy and identifies current challenges and future research priorities.

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conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

46.Whole genome sequencing for tuberculosis disease species identification, lineage determination, and drug resistance detection in Kashgar prefecture, China.

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BACKGROUND: We aimed to use whole genome sequencing (WGS) to determine species and lineage composition and drug resistance profile in a high tuberculosis (TB)-burden region of China.
METHODS: We conducted WGS to 1791 acid-fast staining positive and culture-positive isolates collected from Kashgar prefecture in 2020. Bioinformatic analysis was applied to confirm species, lineage and drug resistant-related mutations. The drug susceptibility testing was performed on confirmed Mycobacterium tuberculosis complex (MTBC) isolates. We determined the accuracy of WGS prediction by comparing with phenotypes.
RESULTS: 95.03% (1702/1791) were identified MTBC, 3.18% (57/1791) were nontuberculous mycobacteria (NTM), 0.61% (11/1791) were nocardia, 0.89% (16/1791) were gordonia and 0.056% (1/1791) were rhodococcus, the rest 4 isolations were identified as mixed infection. MTBC were composed of lineage 2 (45.83%, 780/1702), lineage 3 (462/1702, 27.14%), lineage 4 (455/1702, 26.73%), lineage 1(1/1702, 0.06%) and M.bovis (La1, 4/1702, 0.24%). Resistance to rifampicin, ethambutol, fluoroquinolones, aminoglycosides and ethionamide were accurately predicted with sensitivity of 96.43%, 83.33%,100%, 100% and 94.74% by WGS, while resistance to isoniazid with the sensitivity of 81.62%.
CONCLUSIONS: WGS can be an important approach in assessing TB control strategy

and for determining therapeutic schemes in high TB-burden regions. The drug resistance TB of Kashgar prefecture is at low level and the application of WGS may prevent the increase of resistance rate.

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Conflict of interest statement: Declarations. Ethics approval and consent to participate: Approval to conduct this study was granted by the Tuberculosis Research Ethics Review Committee of the China CDC. Written informed consent was obtained from each participant. Consent for publication: Not applicable. Competing interests: The authors declare no competing interests.

47. Mechanisms of Antibiotic Resistance and Novel Therapeutic Approaches for Mycobacterium tuberculosis: A Narrative Review With a Focus on Tuberculosis Mutations in Iran.

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BACKGROUND AND AIMS: Tuberculosis, caused by Mycobacterium tuberculosis (M.

tuberculosis), is a highly contagious disease and one of the leading causes of mortality globally. The emergence and dissemination of multidrug-resistant (MDR) strains of M. tuberculosis have become a major concern, especially in developing countries. Antibiotic resistance in bacteria constitutes a substantial threat to human health, both now and in the future. The current treatment regimens for tuberculosis are challenging and demanding. Consequently, understanding the antibiotic resistance mechanisms of M. tuberculosis is of paramount importance for global health. This review provides a comprehensive overview of the present state of M. tuberculosis antibiotic resistance by elucidating the underlying mechanisms and presenting up-to-date information and findings in the field. It also highlights deficiencies and challenges in existing studies, with particular emphasis on tuberculosis mutations in the Iranian studies. Furthermore, the study investigate into contemporary global treatment modalities and illuminates new therapeutic avenues for tuberculosis management.
METHOD: This study conducts a review of the literature on M. tuberculosis and its antibiotic resistance, using databases such as Scopus, Embase, MEDLINE/PubMed, Web of Science, and Google Scholar.
RESULTS: The current status of antibiotic resistance in M. tuberculosis represents a serious threat to global health. MDR and extensively drug-resistant (XDR) strains of M. tuberculosis are becoming increasingly widespread.
CONCLUSION: The increasing antibiotic resistance in M. tuberculosis constitutes a significant global health threat, with MDR and XDR strains becoming more prevalent. Effective responses require the development of novel therapeutic drugs, ensuring patients complete their full drug treatment courses, implementing innovative strategies to prevent resistance, and accelerating the creation of effective compounds. Large-scale studies on diverse populations are essential to develop comprehensive solutions and combat the spread of resistance in tuberculosis. Urgent and coordinated efforts are needed to enhance treatment efficacy and control the spread of drug-resistant TB.

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PMID: 41080037

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48. Hierarchical integration of mNGS, PCR, and other conventional methods for precision TB diagnostics.

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This study systematically compared the diagnostic accuracy of seven assays for detecting the Mycobacterium tuberculosis complex, including metagenomic next-generation sequencing (mNGS), droplet digital polymerase chain reaction, real-time quantitative polymerase chain reaction, EasyNAT MTC, GeneXpert MTB/RIF, interferon-gamma release assay (IGRA), and acid–fast staining (AFS). We try to select appropriate combinations of tuberculosis (TB) detection methods for regions with varying levels of medical resources, based on sensitivity, cost-effectiveness, and operational feasibility. A retrospective analysis was conducted on 141 samples collected from patients with suspected active TB at The First Affiliated Hospital of Sun Yat-sen University between April 2022 and April 2024. Among these samples, there were 100 cases assigned to the case group and 41 cases to the control group, based on the tuberculosis diagnostic criteria. Historical data for Xpert, IGRA, and AFS were collected, and parallel experiments using mNGS, droplet digital PCR (ddPCR), real-time quantitative polymerase chain reaction (RT-qPCR), and EasyNAT were conducted on all samples. Diagnostic performance was evaluated by comparing it with the final clinical diagnoses. Sensitivity, specificity, positive predictive value, negative predictive value, and receiver operating characteristic (ROC) curve analysis were conducted, along with DeLong tests for statistical comparison. Compared with the final clinical diagnosis, mNGS demonstrated the highest sensitivity (100%), followed by IGRA (79.2%), EasyNAT (79.1%), RT-qPCR (78.0%), ddPCR (75.8%), Xpert (75.3%), and AFS (16.7%). The specificity was 100% for both Xpert and AFS, followed by ddPCR (97.6%), RT-qPCR (95.1%), EasyNAT (92.7%), IGRA (72.7%), and mNGS (75.6%). ROC analysis revealed a significantly greater area

under the ROC curve for mNGS (0.878) than for ddPCR (0.817, P = 0.031). DeLong tests revealed statistically significant differences in diagnostic performance between mNGS and ddPCR (P < 0.05) and between IGRA and AFS (P < 0.01). mNGS uniquely identified the pathogens involved in co-infection and quantified pathogen-specific sequencing reads. Through a comprehensive evaluation of the diagnostic efficacy, cost-effectiveness, and timeliness of tuberculosis detection methods, we propose corresponding combinations of TB testing approaches for regions with different healthcare resources. For undeveloped regions with limited resources, a combination of AFS +EasyNAT + chest X-ray is recommended. Primary care facilities may additionally employ IGRA + RT-qPCR. Intermediate-level hospitals can incorporate Xpert MTB/RIF for drug resistance testing, while tertiary hospitals or specialized centers should, on the basis of these fundamental tests, utilize mNGS for diagnosis and ddPCR for therapeutic monitoring in patients with complex mixed infections.
IMPORTANCE: This study is the first to comprehensively evaluate the diagnostic efficacy, cost-effectiveness, and timeliness of seven TB detection methods in a single-center cohort. Our findings provide actionable solutions for optimizing TB diagnostics in diverse healthcare ecosystems, aligning with the WHO's End TB Strategy to ensure equitable access to rapid diagnostics.

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49. Application of engineered CRISPR/Cas12a variants with altered protospacer adjacent motif specificities for the detection of isoniazid resistance mutations in Mycobacterium tuberculosis.

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Drug-resistant tuberculosis (TB) is a major global public health concern. Although isoniazid is currently considered one of the most effective first-line drugs for TB treatment, its efficacy is limited by the emergence of resistance. Therefore, it is imperative to develop new methods for detecting drug-resistant TB. In this study, we developed a nucleic acid detection system based on the clustered regularly interspaced short palindromic repeat (CRISPR) Cas12a_RR protein. The system combines recombinase polymerase amplification with an engineered CRISPR/Cas12a_RR protein to enable rapid and specific detection of the katG G944C mutation in isoniazid-resistant Mycobacterium tuberculosis (Mtb). It could detect the target DNA at concentrations as low as 1% in a mixed sample. Compared with TaqMan quantitative polymerase chain reaction and DNA sequencing, the CRISPR/Cas12a_RR system demonstrated superior detection performance in terms of sensitivity, specificity, and cost-effectiveness. Furthermore, it effectively differentiated between drug-resistant Mtb strains from wild-type Mtb strains in clinically isolated samples, with the entire detection process completed in 60 min. In conclusion, the CRISPR/Cas12a_RR detection system offers a novel, rapid, simple, sensitive, and specific approach for identifying isoniazid-resistant Mtb, with significant potential for clinical application, particularly in resource-limited settings.
IMPORTANCE: This study presents a novel method for detecting isoniazid-resistant Mycobacterium tuberculosis (Mtb) using clustered regularly interspaced short palindromic repeat (CRISPR)/Cas12a mutants, offering rapid detection, cost-effectiveness, and high specificity, and thereby providing a promising new avenue for detecting isoniazid-resistant Mtb.

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50.Acceptability of 100-mg moxifloxacin in children with rifampicin-resistant TB in three high-burden countries.

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eCollection 2025 Oct.

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BACKGROUND: Routinely, a 400-mg tablet of moxifloxacin is used in children with rifampicin-resistant TB (RR-TB), but it has very poor acceptability. We describe the acceptability of a 100-mg dispersible moxifloxacin among children and their caregivers in South Africa, India, and the Philippines.
METHODS: This study is nested in a pharmacokinetics, safety, and acceptability trial of new formulations of clofazimine and moxifloxacin in children with RR-TB. Quantitative and qualitative data were collected at four time points over 24 weeks and were analysed descriptively and thematically.
FINDINGS: Median age of participants (n = 36) was 4.9 years. Children and caregivers from all three countries preferred the dispersible 100-mg moxifloxacin to the routine 400-mg tablet due to the relative ease of administration. The 100-mg formulation was unpalatably bitter. Children who were able to swallow the 100-mg formulation preferred to do so. The smaller size of the 100-mg tablets enhanced their ease of preparation and acceptability, although some older participants experienced the increase in the number of tablets (compared with single 400-mg tablet) as a burden.
CONCLUSION: The 100-mg moxifloxacin dispersible formulation is preferred over 400-mg. Overall, moxifloxacin palatability remains sub-optimal, and there is a

need to further improve the acceptability of RR-TB treatments for children.

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51. Structural and functional analysis of the Mycobacterium tuberculosis MmpS5L5 efflux pump presages increased bedaquiline resistance.

Proc Natl Acad Sci U S A. 2025 Sep 30;122(39):e2516660122. doi: 10.1073/pnas.2516660122. Epub 2025 Sep 23.

Fountain AJ(1)(2)(3), Böhning J(1)(2), McLaughlin SH(1), Morgan TE(1), Edelstein PH(1)(2), Troll M(1)(2), Lamers MH(4), Bharat TAM(1), Luisi BF(3), Ramakrishnan L(1)(2).

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Update of
bioRxiv. 2025 Jun 24:2025.06.24.661325. doi: 10.1101/2025.06.24.661325.

Bedaquiline, an antitubercular drug that targets ATP-synthase, is a key component of a new oral drug regimen that has revolutionized the treatment of multidrug-resistant tuberculosis. Clinical bedaquiline resistance in Mycobacterium tuberculosis has rapidly emerged, primarily due to mutations in the transcriptional repressor Rv0678 that result in upregulation of the resistance-nodulation-division (RND) efflux pump MmpS5/MmpL5 (MmpS5L5). Here, to understand how MmpS5L5 effluxes bedaquiline, we determined the structure of the MmpS5L5 complex using cryo-electron microscopy, revealing a trimeric architecture distinct from the canonical tripartite RND efflux pumps of

gram-negative bacteria. Structure prediction modeling in conjunction with functional genetic analysis indicates that it uses a periplasmic coiled-coil tube to transport molecules across the cell wall. Structure-guided genetic approaches identify MmpL5 mutations that alter bedaquiline transport; these mutations converge on a region in MmpL5 located in the lower portion of the periplasmic cavity, proximal to the outer leaflet of the inner membrane, suggesting a route for bedaquiline entry into the pump. While currently known clinical resistance to bedaquiline is due to pump upregulation, our findings that several MmpL5 variants increase bedaquiline efflux may presage the emergence of additional modes of clinical resistance.

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52. Host-directed therapeutic targets in macrophages and their ligands against mycobacteria tuberculosis.

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Although current combination regimens of antibiotics have significantly improved tuberculosis (TB) cure rates, substantial challenges persist in the global effort to end TB. These include poor patient compliance, the emergence of drug-resistant strains due to prolonged treatments, and the persistence of latent TB infections. Host-directed therapies (HDTs) have emerged as a promising

complementary strategy, leveraging the modulation of host immune responses to combat Mycobacterium tuberculosis (Mtb). Unlike conventional antibiotics, HDTs can enhance therapeutic outcomes by boosting host defense mechanisms, reducing treatment duration and dosage, and minimizing the risk of resistance development. Notably, several HDTs have shown significant efficacy against multidrug-resistant (MDR) Mtb strains, while also mitigating excessive inflammation and lowering relapse rates-achievements that remain elusive with antibiotic regimens alone. This review provides a comprehensive overview of recent advancements in HDTs, focusing on druggable targets and the mechanisms by which these therapies restore or enhance immune functions disrupted by Mtb. By integrating insights into macrophage polarization, metabolic modulation, autophagy promotion, and cell death regulation, HDTs offer innovative and multifaceted approaches to TB treatment. Furthermore, the potential for HDTs to synergize with existing antibiotics underscores their relevance in overcoming current therapeutic limitations. This synthesis aims to inspire further research and development, with the ultimate goal of advancing HDTs as a transformative solution for TB management.

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PMID: 40853278 [Indexed for MEDLINE]

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53. Trends in epidemiological characteristics of pulmonary tuberculosis among children and youth in Chinese mainland from 2019 to 2024: analysis of national surveillance data.

BMC Public Health. 2025 Oct 17;25(1):3518. doi: 10.1186/s12889-025-24582-3.

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BACKGROUND: This study aims to analyze trends in epidemiological characteristics of pulmonary tuberculosis (PTB) among children and youth in mainland China from 2019 to 2024 to support informed policy decisions for TB care and prevention.
METHODS: Data on notified PTB cases were extracted from the National TB Surveillance System along with population information for each province from 2019 to 2024. Age-standardized incidence rate (ASIR) was estimated and stratified by year, age, gender and province. Descriptive analysis examined patient characteristics. The Kruskal-Wallis H and Chi-square tests compared data across years. Temporal trends were analyzed using Joinpoint regression models. The average annual percent change (AAPC) assessed the overall trend, and the annual percent change (APC) evaluated local trend or overall trend when there was no joinpoint (APC = AAPC). Spatial-temporal patterns were explored through spatial autocorrelation analysis and spatial-temporal scan statistics.
RESULTS: From 2019 to 2024, mainland China reported 419,000 new PTB cases, with 90.6% in youth and 9.4% in children. The majority were students (48.3%) and farmers (23.8%). The proportion of ethnic minorities, students, individuals identified through active case finding, drug-resistant TB cases, and those with positive bacteriological tests increased over time. Males outnumbered females, but between ages 9 and 15, females surpassed males. The male-to-female ratio remained stable in children, while in youth, males were consistently more affected. The average ASIR over six years was 17.2 per 100,000. Joinpoint regression showed a significant decrease in ASIR from 24.7 per 100,000 in 2019 to 10.5 per 100,000 in 2024 (AAPC = - 15.98, $P < 0.0001$), with no significant joinpoints. Seasonal peak occurred in late spring and autumn, with a trough in February each year. High PTB clusters persisted in the southwest and northwest, particularly in the southwest, where cases increased. Most provinces showed a decline in ASIR, with the most significant decrease in Xinjiang, while Tibet and Qinghai experienced slower reductions.
CONCLUSION: China has made progress in reducing PTB cases among children and youth. However, disparities remain, particularly in high-risk regions. Targeted interventions addressing social and structural factors, along with enhanced regional monitoring and public health measures, are essential to further reduce incidence.

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54. In vitro investigation of Datura innoxia phytocompounds against Mycobacterium tuberculosis H37Ra strain in association with in silico studies.

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Tuberculosis (TB) is a recurrent and progressive bacterial disease caused by Mycobacterium tuberculosis (Mtb), posing a significant challenge globally due to its drug resistance. This study focuses on identifying natural phytocompounds from the plant Datura innoxia (leaves), which is well known for its biologically active metabolites. Initially, the current study employed in vitro analysis of 20 phytocompounds, revealing that the natural compound 9, o-vanillin, exhibited the best minimal inhibitory concentration (MIC) which was 12.5 µg/mL, and minimal bactericidal concentration (MBC) was 50 µg/mL, all other phytocompounds showing remarkable antitubercular activity against the Mtb H37Ra strain. The molecular docking and simulation also validated the strong affinity and stable binding interactions between compound 9 and target protein kinase. The pharmacokinetic analysis highlighted the suitable oral bioavailability and no significant CYP450 inhibition for the lead compound 9, reducing the risk for

drug-drug interactions. Moreover, the density functional theory analysis of lead compound 9 demonstrated optimal molecular properties, further contributing to the chemical stability and reactivity. Therefore, these results suggest that D. innoxia contains the potent phytocompound o-vanillin, which possesses antitubercular activity and can potentially be used as a drug against TB. However, future studies will focus on in vivo validation and formulation development for clinical applications.

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PMCID: PMC12479965
PMID: 41023414 [Indexed for MEDLINE]

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55. Strategic Modulation of Isoniazid Solubility through Cocrystal Formation for Long-Acting Microneedle Therapy of Tuberculosis.

ACS Appl Mater Interfaces. 2025 Oct 1;17(39):54553-54562. doi: 10.1021/acsami.5c13207. Epub 2025 Sep 4.

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Tuberculosis (TB), caused by Mycobacterium tuberculosis, remains a global health emergency, particularly in low- and middle-income countries. Despite effective pharmacotherapy, prolonged treatment, poor adherence, and drug resistance continue to hinder eradication. Isoniazid (ISZ), a first-line antitubercular drug, is effective but limited by high aqueous solubility and short half-life, necessitating daily administration and causing plasma fluctuations. Considering these limitations, strategies to modulate ISZ solubility without altering pharmacodynamics are therefore of therapeutic interest. In this study, we report the design, synthesis, and characterization of a cocrystal of ISZ with salicylic acid (SA), a GRAS-status coformer with low solubility. Cocrystallization was employed to reduce ISZ solubility, enhancing its potential for sustained release. The ISZ-SA cocrystal was confirmed as a distinct crystalline phase by FTIR, DSC, and PXRD, and subsequently incorporated into dissolving microneedle array patches (MAPs) fabricated from biocompatible polymers via aqueous casting.

These MAPs dissolve after skin insertion, releasing their load into the dermal microenvironment. FTIR confirmed the cocrystal's structural integrity within the polymeric matrix, with no dissociation observed during formulation. In vitro release studies showed that ISZ-SA exhibited a slower, more sustained release compared to pure ISZ. Ex vivo dermatokinetic studies revealed significantly greater deposition of ISZ in epidermis (89%, 171.1 μg) and dermis (90%, 468.3 μg) with the cocrystal versus pure drug (36%, 210.0 μg). Enhanced dermal retention suggests localization within skin layers, acting as a depot for gradual systemic absorption. In contrast, pure ISZ permeated faster but deposited less, underscoring the cocrystal's sustained delivery advantage. This work is among the first demonstrations of pharmaceutical cocrystals integrated into dissolving MAPs for transdermal delivery. Cocrystal engineering combined with MAPs may overcome inherent limitations of hydrophilic drugs like ISZ, enabling long-acting formulations that reduce dosing frequency, improve adherence, and enhance TB treatment outcomes, with potential application to other high-solubility drugs.

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PMCID: PMC12492336
PMID: 40907035 [Indexed for MEDLINE]

56.Accuracy of Machine Learning in Identifying Drug Resistance in Tuberculosis: A Systematic Review and Meta-Analysis.

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BACKGROUND AND AIMS: Machine learning (ML) has shown promise in diagnosing tuberculosis (TB), but systematic evidence on its role in predicting and diagnosing drug-resistant tuberculosis (DR-TB) is lacking. This study integrates

a systematic review and meta-analysis to consolidate ML's performance in DR-TB diagnosis and prediction to promote artificial intelligence in this field.
METHODS: Relevant studies were retrieved from PubMed, Cochrane, Embase, and Web of Science up to August 20, 2025, complemented by a manual search of Google Scholar. Risk of bias was evaluated with PROBAST. A bivariate mixed-effects model pooled accuracy measures, with subgroup analyses stratified by ML tasks (diagnosis and prediction).
RESULTS: Twenty-six studies, including 35,472 participants, were analysed. Diagnostic models outperformed prediction models, with a higher pooled AUC (0.94 vs. 0.87). Deep learning (DL)-based diagnostic models consistently surpassed traditional ML across all key metrics, AUC (0.97 vs. 0.89). In the diagnostic model, internal validation showed superior performance to external validation AUC (0.95 vs. 0.85), and in the predictive model, the overall performance of the model in internal validation is slightly better than that in external validation AUC (0.88 vs. 0.85).
CONCLUSION: ML models, particularly DL, demonstrate high diagnostic efficacy for DR-TB, though performance declines in external data sets. Predictive models show moderate accuracy but remain useful for early risk stratification. Large multi-center validations are needed to ensure robustness and clinical applicability.

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PMID: 41098511

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

57. Diagnostic accuracy of low-complexity, manual nucleic acid amplification tests for the detection of pulmonary and extrapulmonary tuberculosis in adults and adolescents: a systematic review and meta-analysis∗.

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BACKGROUND: Low-complexity, manual nucleic acid amplification tests, such as loop-mediated isothermal amplification for tuberculosis (TB-LAMP), are among the molecular WHO-recommended rapid diagnostics and can provide results within a few hours, even in resource-limited settings. We aimed to synthesise evidence on the accuracy of these tests for the detection of pulmonary and extrapulmonary tuberculosis, to inform the 2024 update of the WHO consolidated guidelines on tuberculosis.
METHODS: For this systematic review and meta-analysis, we searched the Cochrane Central Register of Controlled Trials, MEDLINE, Embase, the Science Citation Index and BIOSIS previews, WHO Global Index Medicus, and Scopus databases, for articles published from Jan 1, 1946, to Oct 2, 2023, using specific search terms such as "Tuberculosis", "mycobacterium tuberculosis", "pulmonary tuberculosis", "extrapulmonary tuberculosis", "Loopamp", "diagnostic test", "smear microscopy", and "TB-LAMP". We also examined the reference lists of the included articles to identify potentially eligible studies that were not found in the electronic searches. Additionally, we searched ClinicalTrials.gov and the WHO Clinical Trials Registry Platform for ongoing and unpublished studies. We also examined studies and data received through a WHO public call, made between Nov 30, 2023, and Feb 15, 2024, for eligibility. We included studies that evaluated design-locked, marketed technologies belonging to the class of low-complexity, manual nucleic acid amplification tests (ie, TB-LAMP) against microbiological or composite reference standards, in adults and adolescents (aged ≥10 years) with presumptive pulmonary or extrapulmonary tuberculosis. We excluded studies with case-control designs and those that used in-house methods, screening studies aimed at identifying individuals with active tuberculosis in community settings, and drug-resistance surveys. We extracted data using a standardised form and assessed risk of bias and applicability using the revised Quality Assessment of Diagnostic Accuracy Studies tool. We contacted study authors for further information and data as required. We conducted meta-analyses using bivariate random-effects models to estimate summary sensitivities and specificities for detecting pulmonary and extrapulmonary tuberculosis, and assessed the certainty of evidence using the GRADE approach. This study is registered with PROSPERO, CRD42023471548.

FINDINGS: Our searches identified 2806 records from databases and seven records from other sources. Of these, we screened the full text of 151 articles and ultimately included 29 studies in our systematic review: 27 on pulmonary tuberculosis and three on extrapulmonary tuberculosis (one study evaluated both). The studies generally had low risk of bias and applicability concern. From 26 studies involving 18 297 participants, the summary sensitivity for the detection of pulmonary tuberculosis from respiratory specimens was 84·1% (95% CI 78·3-88·6) and the summary specificity was 96·1% (95% CI 94·2-97·4), both with high certainty of evidence. Three studies, involving 95 participants, assessed the accuracy of TB-LAMP for detecting lymph node tuberculosis using lymph node tissue from biopsy. The summary sensitivity was 94·3% (79·8-98·6) and the summary specificity was 90·0% (79·5-95·4), both with low certainty of evidence.
INTERPRETATION: TB-LAMP has satisfactory performance for detecting pulmonary tuberculosis in adolescents and adults and is a potential alternative to molecular tests that require more advanced infrastructure. However, the inability to detect rifampicin resistance is an important limitation of TB-LAMP. Future research should focus on well powered studies to establish the diagnostic accuracy of TB-LAMP for extrapulmonary tuberculosis sites.
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58. Evaluation of integration in WHO's tuberculosis, HIV, and antimicrobial resistance policies through the social-ecological lens.

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BACKGROUND: TB, HIV, and AMR are closely related global health challenges. In the context of limited global health funds and insufficient resources, an integrated tuberculosis, HIV and antimicrobial resistance prevention and control method will play an important role in the optimization of resources and cost-effectiveness.
OBJECTIVE: This study aims to analyze the degree of policy integration for issues of tuberculosis, HIV and antimicrobial resistance in global health strategies and make recommendations for improving global health governance on related issues.
METHODS: We conducted a thorough analysis of global health policy documents from January 2015 to February 2024, using both quantitative and qualitative approaches. Our focus was on assessing the integration effectiveness of current global health governance mechanisms in addressing tuberculosis, HIV, and antimicrobial resistance from the global governance view based on the content analysis through word frequency analysis and thematic framework analysis. Besides, we conduct a thematic framework analysis of the action plans and policy recommendations outlined in the most recent reports from UNAIDS, Stop TB, and UNEP on HIV, TB and AMR.
RESULTS: The analysis revealed that most documents address TB, HIV, and AMR in isolation, with limited integration and intersectionality. TB and HIV are more frequently linked, while AMR is less associated with the other two. The proposed action lacks specific provisions for joint implementation or monitoring of the evaluation. Additionally, no documented comprehensive overview includes the overall framework of three health priorities.
CONCLUSIONS: The study found that the current global health governance mechanism is significantly inadequate in dealing with integration solutions among tuberculosis, HIV and antimicrobial resistance. So we propose establishing integrated governance and coordination mechanisms for the same population at both horizontal and vertical levels, including individual, interpersonal, community, institutional, and societal levels, and developing an integrated policy framework to facilitate better resolution to address the association between TB, HIV infection and antimicrobial resistance in a resource-limited context.
CLINICAL TRIAL NUMBER: Not applicable.

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59. Predisposing, enabling, and need factors influencing rapid uptake of the world health organization-endorsed TB diagnostic technologies in Africa.

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BACKGROUND: Rapid tuberculosis (TB) diagnostics are essential for TB control. Factors influencing the uptake of these technologies in Africa are not

well-documented for all technologies and are completely undocumented for some countries. We conducted a survey to collect the status and document Predisposing, Enabling, and Need (PEN) factors influencing uptake so that we understand the associated barriers and inform interventions to improve the uptake.
METHODS: We designed, piloted, and distributed a survey questionnaire in January 2023 to the National TB Programme (NTP) and National TB Reference Laboratory (NTRL) managers as well as key partners of the Ministry of Health in the 47 Member States of the World Health Organization African Region (WHO/AFR). Responses were accepted until July 2023. We performed quantitative data analysis using STATA version 14.0.
RESULTS: From the 47 eligible countries, 22 responses (47%) were received from the NTRL managers, 17 (36%) from Technical Assistants (TAs) for NTRL and NTP, and 8 (17%) from the NTP managers. Our findings showed that it took between two to nine years from the endorsement of a new technology to its full implementation, with the duration increasing with the complexity of the test. Laboratory preparedness, staff competence, and policy reform were the main predisposing factors; availability of funds was the primary enabling factor, whereas the emergence of MDR-TB was the key need factor. Good governance and political commitment aligned with the existence of the Directorate of Laboratory Services and the NTRL, were crucial facilitators driving the adoption, adaptation, and implementation.
CONCLUSION: Our findings demonstrated that the uptake of TB diagnostics in Africa is slow. Considering the laboratory preparedness, staff competence, policy reform, availability of funds, and the emergence of MDR-TB as the main PEN factors identified could help speed up the uptake and rapid implementation of any new technology.

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60. Estimating the undetected burden and the likelihood of strain persistence of drug-resistant Neisseria gonorrhoeae.

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Neisseria gonorrhoeae has developed resistance to all antibiotics recommended for treatment, and reports of reduced susceptibility to ceftriaxone, the last-line treatment, are increasing. Because many asymptomatic infections remain undiagnosed and most diagnosed infections do not undergo antibiotic susceptibility testing, surveillance systems may underestimate resistant infections. In this modeling study, we simulated the spread of a new strain of ceftriaxone-nonsusceptible N. gonorrhoeae in a population comprising men who have sex with men as well as heterosexual men and women. We compared scenarios with varying strain characteristics and surveillance capacity. For each scenario, we estimated 1) the number of undetected infections of the novel strain and 2) the likelihood of strain persistence in the absence of newly reported cases. Upon detection of 1 nonsusceptible isolate, the undetected burden was an estimated 5.4 infections with substantial uncertainty (95% uncertainty interval, 0-18 infections). Without additional reports of nonsusceptible infections over the subsequent 180 days, the estimate declined to 2.5 infections (95% uncertainty interval, 0-10). The likelihood of ongoing transmission also declined from 66% (95% uncertainty interval, 26-86) at first detection to 2% (95% uncertainty interval, 0-10) after 180 days. To extend the useful lifespan of last-line antibiotics, our model estimated the infection landscapes that could underlie data from surveillance systems.

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PMCID: PMC12527230
PMID: 39673766 [Indexed for MEDLINE]

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61. Sustainable Antiparasitic Agents from an Agro-Industrial Waste: Mitochondria-Targeting Cashew Nutshell Liquid-Derived Phosphonium and Ammonium Salts.

J Med Chem. 2025 Sep 25;68(18):19438-19462. doi: 10.1021/acs.jmedchem.5c01617. Epub 2025 Sep 8.

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Innovative, sustainable therapies are urgently needed for neglected vector-borne parasitic diseases. In this study, we leveraged cashew nutshell liquid (CNSL), an agro-industrial byproduct, to develop biobased phosphonium and ammonium salts (5-25) targeting parasite mitochondria. By combining CNSL-derived C8 alkyl chains with lipophilic cations, we synthesized novel compounds exhibiting highly potent in vitro and ex vivo activity against Trypanosoma and Leishmania spp., including veterinary-relevant strains like T. b. evansi and T. b. equiperdum. Compounds 5 and 7 outperformed reference drugs, demonstrating subnanomolar efficacy against Trypanosoma brucei spp., high selectivity indices (>1000), and no cross-resistance with current therapies, underscoring their potential as next-generation antitrypanosomal agents. Reduced activity against T. brucei overexpressing alternative oxidase and against Trypanosoma congolense supports a mitochondrial mechanism. Preliminary bioassays in zebrafish and Daphnia magna indicated ecotoxicity lower than antiparasitic activity. These CNSL-derived agents represent promising, environmentally safer antiparasitic candidates aligned with One Health and Green Chemistry principles.

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PMID: 40920168 [Indexed for MEDLINE]

62. Bioactive Compounds Discovery from French Guiana Plant Extracts Through Antitubercular Screening and Molecular Networking.

Plants (Basel). 2025 Sep 30;14(19):3028. doi: 10.3390/plants14193028.

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Tuberculosis (TB) is still a significant public health threat, with rising drug resistance and high incidence in multiple areas worldwide. In the search for novel antitubercular agents, this study explores the application of a bioactivity-guided molecular networking approach to identify bioactive compounds from seven plant species (Curatella americana, Davilla nitida, Dipteryx punctata, Indigofera suffruticosa, Quassia amara, Tetradenia riparia, and Zingiber zerumbet) collected in French Guiana. Using ultrasound-assisted extraction followed by liquid-liquid partitioning and UHPLC-HRMS/MS analysis, a library of 72 samples was tested against Mycobacterium tuberculosis. The non-polar fractions from Indigofera suffruticosa, Tetradenia riparia, and Zingiber zerumbet showed the highest activity. The integration of metabolomic and bioassay data on molecular networks allowed the prioritization and annotation of active compounds, revealing flavonoids as contributors to the antitubercular activity of the active samples. In addition, the use of computational tools such as GNPS, SIRIUS, and TIMA-R enabled dereplication and increased the confidence in the structural prediction of active metabolites. This approach demonstrated its potential in accelerating the identification of both known and novel bioactive compounds without requiring exhaustive isolation, offering a robust strategy for natural product-based drug development against TB.

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PMCID: PMC12526154
PMID: 41095169

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63. Prevalence and distribution patterns of drug resistance in Mycobacterium tuberculosis to first-line antituberculosis drugs in Urumqi, China.

Microbiol Spectr. 2025 Oct 7;13(10):e0137025. doi: 10.1128/spectrum.01370-25. Epub 2025 Sep 3.

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This study aimed to investigate the epidemic status and distribution characteristics of drug-resistant Mycobacterium tuberculosis in Urumqi. From January 2019 to July 2024, all sputum culture-positive Mycobacterium tuberculosis strains were collected in Urumqi. Using the traditional solid-state proportion method for drug-sensitivity testing, we determined the resistance of Mycobacterium tuberculosis to first-line antituberculosis (TB) drugs. The epidemic status and distribution characteristics of first-line antituberculosis drug-resistant Mycobacterium tuberculosis were analyzed using R statistical software (version 3.6.1). Among the 1,241 culture-positive Mycobacterium tuberculosis strains included in this analysis, 973 (78.40%) were smear positive. The overall proportion of non-tuberculous mycobacteria was 2.5%. The overall prevalence of drug-resistant tuberculosis (DR-TB) was 18.93%, with a prevalence of 17.78% in new cases and 24.40% in retreatment cases, respectively. In this survey, the overall prevalence was 10.91% (132 out of 1,210) for mono-drug-resistant tuberculosis, 3.72% (45 out of 1,210) for polydrug-resistant tuberculosis, and 4.30% (52 out of 1,210) for multidrug-resistant tuberculosis. Moreover, the patterns of resistance to first-line anti-TB drugs were highly diverse. The drug-resistance rate among retreatment tuberculosis patients in Urumqi remains notably high. Thus, enhancing drug-resistance surveillance in these patients is critical for effective tuberculosis prevention and control in the region.

IMPORTANCE: The result of this study indicated that DR-TB is a serious public health problem in Urumqi. Resistance drugs distributed type to first-line anti-TB drugs are very broad in Urumqi. Any resistance to anti-TB drugs in new cases is more than in retreatment cases.

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PMID: 40899878 [Indexed for MEDLINE]

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64. Diagnostics and new treatment regimens for TB: can the Xpert MTB/XDR assay fill the gap for fluoroquinolone testing?

J Clin Microbiol. 2025 Oct 8;63(10):e0064325. doi: 10.1128/jcm.00643-25. Epub 2025 Sep 3.

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Rapid diagnosis of resistance-conferring mutations to antibiotics used for the treatment of tuberculosis (TB) is critical for patient care and public health control efforts. Prior guidelines included the use of fluoroquinolones (FQs) for the treatment of drug-resistant TB, including multidrug-resistant TB, pre-extensively drug-resistant TB, and extensively drug-resistant TB. More recently, a short-course regimen for antibiotic-susceptible TB was introduced, which includes the use of a FQ, a drug class that diagnostic algorithms in the United States (US) typically do not test for if all first-line agents are susceptible. However, FQ mono-resistance has been documented by previous studies, and for this reason, we tested 319 archived Mycobacterium tuberculosis complex (MTBC) strains spanning a 14-year period of time using the Xpert MTB/XDR assay. Resistance to FQs was detected in 4.4% (14/319) of the isolates tested, with mutations predominating in the gyrA region (13/14; 92.9%). A single isolate (1/14; 7.1%) was found to have a gyrB mutation. A broth microdilution assay demonstrated the minimum inhibitory concentrations for resistant strains that ranged from 0.5 µg/mL to 8.0 µg/mL. Importantly, three strains were FQ mono-resistant and would have been completely missed by standard testing algorithms. Although currently unavailable in the US, the GeneXpert XDR assay has the potential to fill the significant diagnostic gap in susceptibility

testing of MTBC resistance to FQs and support the use of the currently recommended short-course regimen.IMPORTANCE This study provides insight into the need for additional rapid testing for the detection of drug resistance (specifically to fluoroquinolones) in tuberculosis (TB) cases in the United States (US). The current regimens for TB treatment rely on knowing resistance patterns to optimize treatment, and missed resistance could have a negative impact on the health of the patient, as well as contribute to increased drug-resistance mutations in new TB cases. There are currently limited platforms for expanded rapid drug resistance testing for TB cases in the US, and this study looks at past TB cases that had drug resistance missed by routine testing.

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PMCID: PMC12509795
PMID: 40899881 [Indexed for MEDLINE]

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

65. Identification of potential inhibitors of dihydrofolate reductase (DHFR) through blocking the folate biosynthetic pathway of Mycobacterium tuberculosis utilizing structure-based virtual screening.

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Tuberculosis (TB) has emerged as a leading cause of death due to a single infectious agent-Mycobacterium tuberculosis (Mt). This situation is exacerbated by delayed diagnosis, inadequate administration of effective TB medications, prolonged duration of treatment, shortage of toxin-free TB drugs, and frequent increases in resistance to most TB drugs. In an urge to find potential drug candidates for the treatment of fatal infectious TB disease, we targeted the folate biosynthetic pathway that involves the ubiquitous enzyme dihydrofolate reductase (DHFR), which catalyzes the NADPH-dependent reduction of dihydrofolate with the generation of tetrahydrofolate (THF). Blocking the enzymatic activity of DHFR exhausts the cellular pool of THF, which results in cessation of DNA synthesis in rapidly proliferating cells and ultimately cell death. Herein, a total of 1026 drug-like molecules with antibacterial activities were tested using several in silico tools for determining drug-likeness features, ADMET (absorption, distribution, metabolism, excretion, and toxicity) profiling, binding affinity, and conformation analysis using Autodock Vina and Schrodinger Suite. This exhaustive investigation identified CHEMBL577, CHEMBL161702, and CHEMBL1770248 as potential drug candidates for the inhibition of M. tuberculosis DHFR protein. Root mean square deviation, root mean square fluctuation, hydrogen bond, and MMGBSA evaluation by 100 ns molecular dynamics simulation (MDS) confirmed their molecular stability with the target protein. All of these drug-like compounds outperformed the control drugs trimethoprim and methotrexate in molecular docking and molecular dynamics simulation tests. Therefore, our study suggests these M. tuberculosis DHFR inhibitors as promising drug candidates. However, additional wet-lab experiments are required to verify their potential therapeutic potency as novel drugs against M. tuberculosis.

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PMID: 41041286

Conflict of interest statement: There are no conflicts of interest to declare.

66. Population structure and antibiotic resistance profiles of Mycobacterium tuberculosis isolates from Ibadan, Nigeria (2019-2020): a pilot study to improve affordable molecular diagnostic tools.

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Nigeria ranks as the sixth country globally and the first in Africa with the highest burden of tuberculosis (TB) infection. The emergence and spread of multidrug-resistant TB (MDR-TB) strains have posed significant challenges to effective disease management in the country. In this study, 55 Mycobacterium tuberculosis (MTB) isolates from patients attending a hospital in Ibadan city (Nigeria) were selected. MTB isolates were analyzed using PCR amplification of gene fragments associated with antibiotic resistance, followed by Sanger sequencing and bioinformatics analysis. Additionally, MIRU-VNTR genotyping was performed to address population structure and transmission dynamics. Results show an association between mutations in the rpoB, inhA and gyrA genes and phenotypic resistance to rifampicin, isoniazide and fluoroquinolones in a significant percentage of the MTB isolates. However, an extended panel of genes would enable a better characterization of antibiotic resistance. The population structure of MTB in Ibadan, as determined by using MIRU-VNTR, revealed that 96.1% of the strains belong to lineage 4, distributed in the following sublineages: Uganda I (47.1%), LAM (21.6%), Cameroon (17.6%), and Ghana (9.8%). Meanwhile, 3.9% of the strains correspond to lineage 5 (L5), West African-1 sub-lineage. The population structure was very heterogeneous and no active transmission clusters were detected. Overall, this pilot study demonstrated the utility of cost-effective molecular tools in enhancing TB surveillance and control programs in settings where whole-genome sequencing (WGS) is still an economical challenge.

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Recent TB News

US funding cuts could result in nearly 9 million child tuberculosis cases, 1.5 million child deaths.
https://hsph.harvard.edu/news/u-s-funding-cuts-could-result-in-nearly-9-million-child-tuberculosis-cases-1-5-million-child-deaths/
A new study led by Harvard T.H. Chan School of Public Health and Boston University School of Public Health has provided some of the first extensive estimates of the number of children who are expected to both develop and die from tuberculosis (TB) over the next decade in middle and low income countries if the U.S. continues to cut funds for global health aids. The study focused on collecting national data from 130 lower-middle income countries on TB services, HIV prevalence, and funding sources for related programs to project how different levels of aid would affect different risks pertaining to TB and HIV from 2025 to 2034.

WHO releases new guidelines on tuberculosis and undernutrition
https://www.who.int/news/item/08-10-2025-who-releases-new-guidelines-on-tuberculosis-and-undernutrition
As part of the WHO consolidated guidelines on tuberculosis (Module 6: tuberculosis and comorbidities), the WHO has released new recommendations on tuberculosis and undernutrition. These new guidelines mark a critical step in addressing determinants as part of people-centered care under WHO's End TB Strategy, and with undernutrition being a significant driver of TB, tackling undernutrition and food insecurity among those affected by TB has the potential to improve health outcomes. These guidelines will require close collaboration between government entities and stakeholders but will also contain steps towards improving engagement and coordination.

Expanding TB prevention could save millions of lives and yield major economic benefits, global study finds
https://muhc.ca/news-and-patient-stories/news/expanding-tb-prevention-could-save-millions-lives-and-yield-major
A recent study has shown that expanding TB screening and preventative services in key populations could not only reduce TB incidence but also deliver economic returns. The study utilized modeling to outline the investments required, and the potential benefits, of implementing

screening and preventative services in people living with HIV, household contacts of TB patients, and other more country-specific high-risk groups. The study emphasizes that by implementing interventions that already exist, large societal returns on investment can be generated.