November Literature

PubMed Open Access:

1. Introducing BPaL: Experiences from countries supported under the LIFT-TB project.

PLoS One. 2024 Nov 19;19(11):e0310773. doi: 10.1371/journal.pone.0310773. eCollection 2024.

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BACKGROUND: Previously, drug-resistant tuberculosis (DR-TB) patients were treated with long, toxic, and relatively ineffective regimens. However, in recent years, there have been major improvements made. The 2020 World Health Organization DR-TB Treatment guidelines recommended the use of a 6-months all-oral BPaL (bedaquiline, pretomanid and linezolid) regimen under operational research (OR) conditions for selected DR-TB patients.
METHODS: The processes, challenges, and interim results of introducing BPaL under OR conditions in 7 countries supported under the Korea International Cooperation Agency/TB Alliance-funded "Leveraging Innovation for Faster Treatment of Tuberculosis (LIFT-TB)" project are described here. The OR objectives were to explore the feasibility of introducing the BPaL regimen, and to estimate its effectiveness and safety in a select group of DR-TB patients.
RESULTS: Between November 2020 and the end of March 2023, a total of 574 patients had been enrolled. Interim treatment success stands at an encouraging 90.9% (280/308). Although adverse events of special interest (AESI) were common, they were manageable, and only 1 patient had to discontinue the complete BPaL treatment regimen. In addition, no unexpected adverse events (AE) were seen.

CONCLUSION: With careful advocacy, frequent communication with partners, and following steps to strengthen essential aspects of the delivery system, the project's experiences show that BPaL OR was feasible across different country settings. Project documents were constantly updated. The sharing of information, experiences, and interim results had a significant positive and motivating effect within and across countries. Interim OR results show excellent patient responses and are comparable to those seen under trial conditions. Although common, the observed AEs and AESIs were manageable, and no unexpected AEs were seen.

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Conflict of interest statement: I have read the journal's policy and the following co-authors of this manuscript -S. Foraida, M. Diachenko, and S. Juneja have the following competing interests: Paid employment or consultancy with TB Alliance, the developer of pretomanid. This does not alter our adherence to PLOS ONE policies on sharing data and materials.

2. Endogenous reactivation cases identified by whole genome sequencing of Mycobacterium tuberculosis: Exploration of possible causes in Latvian tuberculosis patients.

J Clin Tuberc Other Mycobact Dis. 2024 Oct 31;37:100493. doi: 10.1016/j.jctube.2024.100493. eCollection 2024 Dec.

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BACKGROUND: The recurrence of tuberculosis (TB) continues to place a significant burden on patients and TB programs worldwide. Repeated TB episodes can develop

either due to endogenous reactivation of previously treated TB or exogenous reinfection with a distinct strain of Mycobacterium tuberculosis (Mtb). Determining the precise cause of the recurrent TB episodes and identifying reasons for endogenous reactivation of previously successfully treated patients is crucial for introducing effective TB control measures.
METHODS: Here, we aimed to provide a retrospective individual analysis of the clinical data of pulmonary TB patients with assumed endogenous infection reactivation based on WGS results to identify the reasons for reactivation. Patient medical files were reviewed to describe the provoking factors for endogenous reactivation.
RESULTS: In total, 25 patients with assumed endogenous TB reactivation were included in the study group, and 30 patients with one TB episode during the study period were included in the control group. There were no statistically significant differences identified between studied patient groups in patients age ($t(53) = -1.53$, $p = 0.13$), body mass index ($t(53) = 0.82$, $p = 0.42$), area of residency ($\chi2$ (1;55) = 0.015, $p = 0.9$), employment status ($\chi2$ (1;55) = 0.076, $p = 0.78$) and presence of comorbidities ($\chi2$ (1;55) = 3.67, $p = 0.78$). Study group patients had statistically significantly more frequently positive sputum smear microscopy results ($\chi2$ (1;55) = 8.72, $p = 0.0031$), longer time to sputum smear ($t(31) = -2.2$, $p = 0.036$) and sputum culture conversion (W (55) = 198.5, $p = 0.0029$). Smoking was statistically significantly ($\chi2$ (1;55) = 5.77, $p = 0.016$) more frequently represented among study group patients. The median treatment duration for drug susceptible TB was 6 months in both in the control group (IQR 6-6) and among study group patients (IQR 6-7.75). The median treatment duration for multidrug-resistant TB was 20 months (IQR 17-23) in the control group and 19 months (IQR 16-19) in the study group patients.
CONCLUSION: Positive SSM for acid-fast bacteria, delayed time to sputum smear and sputum culture conversion, smoking, and incomplete therapy in the study group patients with multidrug-resistant TB should be considered as potential reasons for reactivation in recurrent TB patient group in our study.

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PMID: 39559709

Conflict of interest statement: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

3. Trends of drug-resistant tuberculosis and risk factors to poor treatment-outcome: a database analysis in Littoral region-Cameroon, 2013-2022.

BMC Public Health. 2024 Nov 18;24(1):3195. doi: 10.1186/s12889-024-20585-8.

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INTRODUCTION: Tuberculosis(TB), currently has limited treatment options, and faces worldwide threat of drug-resistance(DR). In 2022, the DR-TB prevalence in Cameroon was 1.4% among new-cases and 8.3% among retreatment-cases. We analyzed the DR-TB database to descript the trends and DR-TB profile, treatment-outcome and associated risk-factors so-as-to propose measures to enhance program performance in Cameroon.
MATERIALS AND METHODS: We conducted a retrospective cohort study, analysed the DR-TB database of the Littoral region from 2013 to 2022. We appreciated the data-quality using zero-reporting, completeness, consistency, and validity indicators. We categorized DR-TB into Rifampicin-resistant-TB(RR-TB), multi-drug-resistant-TB(MDR-TB), pre-extensive-drug-resistant-TB(pre-XDR-TB), and XDR-TB and performed descriptive statistics. We assessed DR-TB treatment outcome targeting > 80% cure and/or completed treatment. Multiple logistic regression was used to determine risk factors related to poor treatment outcomes, and adjusted relative risk(RR) was considered significant at $p < 0.05$.
RESULTS: Overall database quality was 93.7% with uniqueness 100%, data-completeness 82.5%, consistency 97% and validity 95.1%. A total of 567 DR-TB cases were reported, with median age of 34 (1-80) years, male-to-female sex ratio (3:2). Cases were classified as 19(3.4%) RR-TB, 536(94.6%) MDR-TB, 7(1.3%) pre-XDR-TB, and 4(0.7%) XDR-TB. Case-reporting increased from 2013, reaching their peak in 2018. The overall treatment refusal rate was 123(11.9%) and treatment outcomes of 270(60.8%) cured, 116(26.4%) completed, 32(7.2%) deaths, 19(4.3%) lost-to-follow-up, and 6(1.4%) failure were recorded. We identified 84 dead (CFR:14.8%) amongst whom 52(62%) refused treatment, 17(20%) occurred during the first month of therapy and 13(15.5%) HIV-TB co-infected. Male gender [$p = 0.006$, RR = 2.5 (95% CI: 1.3-4.7)], HIV positive status [$p = 0.012$, RR = 2.1 (95% CI: 1.2-3.7)], and previous DR-TB status [$p = 0.02$,

RR = 3.9 (95% CI: 1.3-12.0)] were statistically associated to poor treatment outcomes.
CONCLUSION: In the Littoral Region-Cameroon, cases of DR-TB increased from 2013, reaching their peak in 2018 befor dropping right up to 2022. RR-TB, MDR-TB, Pre-XDR-TB and XDR-TB represented 3.4%, 94.6%, 1.3% and 0.7% of all reported DR-TB cases. Overall, DR-TB treatment success rate was 87.2%. Male-gender, HIV-positive status, and previous DR-TB are associated with poor TB treatment outcomes. We recommend universal drug susceptibility testing to ensure early/maximum DR-TB case-detection and proper pre-treatment counselling to limit the high death rates and anti-TB treatment refusal rates which are setbacks from achieving end-TB strategies.

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Conflict of interest statement: Declarations Consent for publication Not applicable. Competing interests The authors declare no competing interests. Ethical approval and consent to participate Since this was a database analysis where we didn’t have any contact with the patients or their specimens, it wasn’t possible for us to obtain participants’ consent. We also judge it is not obligatory to obtain ethical clearance. We however obtained administrative authorization from the Ministry of Public Health with decision number No04671/L/MINSANTE/SG/CCOUSP to evaluate the drug-resistant tuberculosis database analysis in the Littoral Region-Cameroon, 2013–2022. Participant information was anonymized by assigning a unique protocol number.

4. A Multi Center, Epidemiological Study of Bone Tuberculosis in Southwest China from 2011 to 2023.

J Epidemiol Glob Health. 2024 Nov 18. doi: 10.1007/s44197-024-00325-2. Online ahead of print.

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BACKGROUND: Despite continued efforts to manage and control Tuberculosis (TB) in China, it remains a major health concern. Bone tuberculosis (Bone-TB), a common form of extrapulmonary tuberculosis, still adds considerably to the global TB case load. Diagnosing Bone-TB is often difficult as its symptoms can be similar to other bone or joint diseases, which leads to delayed detection and treatment. Currently, comprehensive reports on the epidemiological aspects of Bone-TB in China are scarce.
METHODS: This retrospective study analyzed demographic and clinical data from 2,191 patients diagnosed with Bone-TB in Southwest China between January 2011 and September 2023.This study fully reveals the characteristics of Bone-TB in Southwest China.
RESULTS: The overall trend of bone tuberculosis was a slow rise. Among 2191 patients, males, farmers, aged 42-68 years, and people with HIV and diabetes are the priority groups for the prevention and treatment of Bone-TB. The majority of the infected spines (1556/2191) were located in the thoracic vertebra (759/2191) and lumbar vertebra (715/2191). Forty-nine (2.24%) patients had drug-resistant TB (DR-TB). Forty-five (2.05%) died during the treatment. The total and actual hospitalization. Costs amounted to $3,837.10 and $1,914.35 ($p < 0.01$). Patients with DR-TB incurred the highest costs, amounting to $4,968.37. Cervical TB, with a prevalence of 5 patients (6.10%), exhibited the highest rates of catastrophic expenditures.
CONCLUSIONS: From 2011 to 2023, the yearly occurrence of Bone-TB in southwestern China exhibited a rising pattern, marked by notable distinctions in terms of gender, age, and regional variations, indicating localized clustering characteristics.

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PMID: 39556304

Conflict of interest statement: Declarations Ethics Approval and Consent to Participate As per the Ethics Committee of the First Affiliated Hospital of Guangxi Medical University and the Fourth People’s Hospital of Nanning, written informed consent from each patient was deemed unnecessary for this study due to the removal of all sensitive patient information prior to analysis. The study adhered to the principles of the Declaration of Helsinki and received approval from the Ethics Committee of the Fourth People’s Hospital of Nanning and the First Affiliated Hospital of Guangxi Medical University (Approval number: 2023-36-01, NO.2022-KY-E-152). Consent for Publication Not applicable. Competing Interests The authors declare no competing interests.

5. Predictive model for aminoglycoside induced ototoxicity.

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BACKGROUND: Irreversible hearing loss is a well-known adverse effect of aminoglycosides, however, inability to accurately predict ototoxicity is a major limitation in clinical care. We addressed this limitation by developing a prediction model for aminoglycoside ototoxicity applicable to the general population.
METHODS: We employed a prospective non-drug-resistant tuberculosis (TB), non-HIV/AIDS cohort of 153 adults on Streptomycin based anti-TB therapy. High frequency pure-tone audiometry was done at regular intervals throughout the study. Clinical and audiological predictors of ototoxicity were collated and ototoxic threshold shift from the baseline audiogram computed. The prediction model was developed with logistic regression method by examining multiple predictors of ototoxicity. Series of models were fitted sequentially; the best model was identified using Akaike Information Criterion and likelihood ratio test. Key variables in the final model were used to develop a logit model for ototoxicity prediction.
RESULTS: Ototoxicity occurred in 35% of participants. Age, gender, weight, cumulative Streptomycin dosage, social class, baseline pure tone average (PTA) and prior hearing symptoms were explored as predictors. Multiple logistic regression showed that models with age, cumulative dosage and baseline PTA were best for predicting ototoxicity. Regression parameters for ototoxicity prediction showed that yearly age increment raised ototoxicity risk by 5% (AOR = 1.05; CI, 1.01-1.09), and a gram increase in cumulative dosage increased ototoxicity risk by 7% (AOR = 1.05; CI, 1.05-1.12) while a unit change in baseline log (PTA) was associated 254% higher risk of ototoxicity (AOR = 3.54, CI: 1.25, 10.01). Training and validation models had area under the receiver operating characteristic curve as 0.84 (CI, 0.76-0.92) and 0.79 (CI, 0.62-0.96) respectively, showing the model has discriminatory ability.
CONCLUSION: This model can predict aminoglycoside ototoxicity in the general

population.

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PMCID: PMC11563990
PMID: 39555479

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.

6. Comparative study on the virulence of mycobacteriophages.

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The global tuberculosis (TB) epidemic affected 10 million people and caused 1.3 million deaths in 2022 alone. Multidrug-resistant TB is successfully treated in less than 60% of cases by long, expensive and aggressive treatments. Mycobacteriophages, viruses that can infect bacteria such as Mycobacterium tuberculosis-the species responsible for TB, have the potential to redefine TB prevention and treatments. However, the development of phage-based products necessitates the assessment of numerous parameters, including virulence and adsorption, to ensure their performance and quality. In this work, we characterized the virulence of three different mycobacteriophages (Fionnbharth, Muddy and D29), alone and as cocktails, against a TB model host (Mycobacterium smegmatis) under planktonic and early-stage biofilm growth conditions. Phage D29

and cocktails containing D29 had the highest virulence under all conditions. Interestingly, phages Fionnbharth and Muddy and their combination showed higher virulence against early-stage biofilm than against the planktonic phenotype. Adsorption assays indicated that all three phages had lower adsorption efficiencies on the early-stage biofilm phenotype than on the planktonic one, suggesting a reduced availability of receptors in the former. Given that, despite these lower adsorption efficiencies, the virulence of the phages and phage cocktails was either unchanged or higher against the early-stage biofilm, this phenotype must display properties that are favorable to other steps of the infection process. These results inform us on the dynamics of mycobacteriophage infections, alone and in cocktail formulations, under different host growth conditions, and serve as a basis for the development of phage products targeting mycobacteria biofilms.

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PMID: 39554140

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

7. Integrated virtual screening and MD simulation study to discover potential inhibitors of mycobacterial electron transfer flavoprotein oxidoreductase.

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Tuberculosis (TB) continues to be a major global health burden, with high incidence and mortality rates, compounded by the emergence and spread of drug-resistant strains. The limitations of current TB medications and the urgent need for new drugs targeting drug-resistant strains, particularly multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB, underscore the pressing demand for innovative anti-TB drugs that can shorten treatment duration. This has led to a focus on targeting energy metabolism of Mycobacterium tuberculosis (Mtb) as a promising approach for drug discovery. This study focused on repurposing drugs against the crucial mycobacterial protein, electron transfer flavoprotein oxidoreductase (EtfD), integral to utilizing fatty acids and cholesterol as a carbon source during infection. The research adopted an integrative approach, starting with virtual screening of approved drugs from the ZINC20 database against EtfD, followed by molecular

docking, and concluding with molecular dynamics (MD) simulations. Diacerein, levonadifloxacin, and gatifloxacin were identified as promising candidates for repurposing against TB based on their strong binding affinity, stability, and interactions with EtfD. ADMET analysis and anti-TB sensitivity predictions assessed their pharmacokinetic and therapeutic potential. Diacerein and levonadifloxacin, previously unexplored in anti-tuberculous therapy, along with gatifloxacin, known for its efficacy in drug-resistant TB, have broad-spectrum antimicrobial properties and favorable pharmacokinetic profiles, suggesting potential as alternatives to current TB treatments, especially against resistant strains. This study underscores the efficacy of computational drug repurposing, highlighting bacterial energy metabolism and lipid catabolism as fruitful targets. Further research is necessary to validate the clinical suitability and efficacy of diacerein, levonadifloxacin, and gatifloxacin, potentially enhancing the arsenal against global TB.

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PMID: 39546486 [Indexed for MEDLINE]

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

8. Experience of piloting BPaLM/BPaL for DR-TB care at selected sites in Pakistan.

IJTLD Open. 2024 Nov 1;1(11):508-515. doi: 10.5588/ijtldopen.24.0369. eCollection 2024 Nov.

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BACKGROUND: Pakistan ranks fourth globally in terms of high drug-resistant TB (DR-TB) burden, with approximately one-third of cases resistant to fluoroquinolones. Bedaquiline, pretomanid, linezolid and moxifloxacin

(BPaLM/BPaL) offers an opportunity for most DR-TB patients to benefit from a shorter, all-oral, well-tolerated and more effective treatment.
METHODS: We conducted a retrospective cohort study to pilot the BPaLM/BPaL regimen at four selected sites in two provinces of Pakistan, i.e. Punjab and Khyber Pakhtunkhwa. Data were extracted and analysed using electronic medical records from the program. Descriptive statistics, survival analysis and binary logistic regression analysis were employed.
RESULTS: A total of 116 patients took treatment between October 2022 and February 2023. The treatment success rate was 96%, with 3% deaths and <1% loss to follow-up. Patients typically completed treatment in 26.2-26.7 weeks for BPaLM and BPaL, respectively. No serious adverse events were observed. The most common side effects included QTcF prolongation (BPaLM: 55%, BPaL: 84%), haematological events (BPaLM: 32%, BPaL: 34%), and gastrointestinal problems (BPaLM: 36%, BPaL: 25%).
CONCLUSION: The BPaLM/BPaL regimens for DR-TB are highly effective with minimal adverse events and feasible to implement in routine program circumstances.

Publisher: CONTEXTE: Le Pakistan occupe la quatrième position mondiale concernant la prévalence de la TB résistante aux médicaments (DR-TB, pour l'anglais « drug-resistant TB »), avec près d'un tiers des cas présentant une résistance aux fluoroquinolones. Les traitements comprenant la bédaquiline, le prétomanid, le linézolide et la moxifloxacine (BPaLM/BPaL) permettent à la majorité des patients atteints de DR-TB de bénéficier d'une thérapie plus courte, entièrement orale, bien tolérée et plus efficace.
MÉTHODES: Nous avons réalisé une étude de cohorte rétrospective afin d'évaluer le régime BPaLM/BPaL dans quatre sites choisis au sein de deux provinces du Pakistan, à savoir le Punjab et le Khyber Pakhtunkhwa. Les données ont été collectées et examinées à partir des dossiers médicaux électroniques du programme. Des statistiques descriptives, une analyse de survie ainsi qu'une analyse de régression logistique binaire ont été appliquées.
RÉSULTATS: Un total de 116 patients a reçu un traitement entre octobre 2022 et février 2023. Le taux de succès du traitement s'élevait à 96%, avec 3% de décès et moins de 1% de patients perdus de vue. En moyenne, les patients ont complété le traitement en 26,2 à 26,7 semaines pour les protocoles BPaLM et BPaL, respectivement. Aucun événement indésirable grave n'a été rapporté. Les effets secondaires les plus courants comprenaient l'allongement de l'intervalle QTcF (BPaLM : 55%, BPaL : 84%), des événements hématologiques (BPaLM : 32%, BPaL : 34%) et des troubles gastro-intestinaux (BPaLM : 36%, BPaL : 25%).
CONCLUSION: Les protocoles BPaLM/BPaL pour la DR-TB se révèlent particulièrement efficaces, présentant peu d'effets secondaires, et peuvent être intégrés dans un programme de soins standard.

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Conflict of interest statement: Conflict of interest: SF, AG and SJ are employed by TB Alliance, the non-profit product development partnership that developed pretomanid and the BPaL regimen for treating drug-resistant TB.

9. Updated treatment guidelines for drug-resistant TB: how safe are clofazimine-based regimens?

IJTLD Open. 2024 Nov 1;1(11):486-489. doi: 10.5588/ijtldopen.24.0490. eCollection 2024 Nov.

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In June 2024, WHO released 'Key updates to the treatment of drug-resistant tuberculosis: rapid communication', after the preliminary publication of results from two clinical trials: 'BEAT-Tuberculosis' and 'endTB'. All proposed regimens include clofazimine (Cfz). However, a recent paper has reported a high incidence of QTc prolongation among patients receiving Cfz-based treatment for multidrug-resistant TB in Taiwan. Here, we discuss the cardiac safety of Cfz and the role of active drug safety monitoring at the programme level in collecting information on this issue.

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PMID: 39544882

10. Treatment outcomes and associated factors among patients with multidrug-resistant tuberculosis in Southwestern Oromia, Ethiopia: ten-year retrospective analysis.

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BACKGROUND: Treatment of rifampicin-resistant or multidrug-resistant tuberculosis (RR/MDR-TB) requires the use of second-line anti-TB drugs, which are less effective and more toxic. This study assessed treatment outcomes and factors associated with unfavorable treatment outcomes among RR/MDR-TB patients in Southwestern Oromia, Ethiopia.
METHODS: A multicenter retrospective study was conducted on 226 RR/MDR-TB patients (six extrapulmonary and 220 pulmonary) treated under a national TB program between 2013 and 2022 at five treatment facilities in Southwestern Oromia, Ethiopia. RR/MDR-TB patient data, such as sociodemographic, clinical, and laboratory results and treatment outcomes, were collected from the RR/MDR-TB registry using a standard data extraction form between April and June 2023. Logistic regression analysis was used to explore the associations between risk factors and unfavorable treatment outcomes.
RESULTS: Among 220 pulmonary RR/MDR-TB patients, 181 (82.3%) achieved favorable treatment outcomes (161 cured and 20 treatment completed). However, 39 (17.7%) patients had unfavorable treatment outcomes (12 were lost to follow-up, seven experienced treatment failure, and 20 died). Of the six extrapulmonary RR/MDR-TB patients, five (83.3%) had favorable treatment outcomes, and one (16.7%) was lost to follow-up. Pulmonary RR/MDR-TB patients with HIV infection (AOR = 4.85, 95% CI: 1.90 to 12.39), history of previous TB treatment (AOR = 3.09, 95% CI: 1.21 to 7.86), and low baseline BMI (AOR = 2.86, 95% CI: 1.06 to 7.72) had increased risk of unfavorable treatment outcomes.
CONCLUSION: Although the majority of RR/MDR-TB patients have favorable treatment outcomes, a significant proportion of patients still experienced unfavorable outcomes. Patients with HIV infection, history of previous TB treatment, and low baseline BMI require special attention to improve pulmonary RR/MDR-TB treatment outcomes. Future studies with larger sample sizes are required to evaluate treatment outcomes and associated factors among patients with extrapulmonary RR/MDR-TB.

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PMID: 39543471 [Indexed for MEDLINE]

Conflict of interest statement: Declarations Ethical approval and consent to Participate The study was performed following the principles stated in the Declaration of Helsinki. The Institutional Review Board (IRB) at the Institute of Health, Jimma University, Ethiopia, approved the study protocol (Reference No. IHRPG/169/21) and waived the requirement for informed consent due to the

retrospective nature of the study design. To ensure the privacy and confidentiality of the study participants, the data were deidentified and securely stored in locked cabinets. Consent for publication Not applicable. Competing interests The authors declare no competing interests.

11. Modeling the epidemiologic impact of age-targeted vaccination for drug-resistant tuberculosis.

Drug Resist Updat. 2024 Nov 13;78:101172. doi: 10.1016/j.drup.2024.101172. Online ahead of print.

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This study used a calibrated mathematical model to evaluate age-specific tuberculosis (TB) vaccination strategies, for drug-resistant (DR)-TB management in China. Prioritizing elderly vaccination significantly reduced multidrug-resistant or rifampicin-resistant TB incidence and mortality, while avoiding the need for second-line treatment, offering a promising approach to mitigate DR-TB burden by 2050.

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PMID: 39541911

Conflict of interest statement: Declaration of Competing Interest The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

12. Catalase activity deficiency sensitizes multidrug-resistant Mycobacterium tuberculosis to the ATP synthase inhibitor bedaquiline.

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Multidrug-resistant tuberculosis (MDR-TB), defined as resistance to the first-line drugs isoniazid and rifampin, is a growing source of global mortality and threatens global control of tuberculosis disease. The diarylquinoline bedaquiline has recently emerged as a highly efficacious drug against MDR-TB and kills Mycobacterium tuberculosis by inhibiting mycobacterial ATP synthase. However, the mechanisms underlying bedaquiline's efficacy against MDR-TB remain unknown. Here we investigate bedaquiline hyper-susceptibility in drug-resistant Mycobacterium tuberculosis using systems biology approaches. We discovered that MDR clinical isolates are commonly sensitized to bedaquiline. This hypersensitization is caused by several physiological changes induced by deficient catalase activity. These include enhanced accumulation of reactive oxygen species, increased susceptibility to DNA damage, induction of sensitizing transcriptional programs, and metabolic repression of several biosynthetic pathways. In this work we demonstrate how resistance-associated changes in bacterial physiology can mechanistically induce collateral antimicrobial drug sensitivity and reveal druggable vulnerabilities in antimicrobial resistant pathogens.

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PMID: 39537610 [Indexed for MEDLINE]

Conflict of interest statement: Competing interests J.J.C. is a co-founder and board member of Phare Bio, a nonprofit venture focused on antibiotic drug development. P.C.B. is a consultant to or holds equity in 10X Genomics, General Automation Lab Technologies/Isolation Bio, Celsius Therapeutics, Next Gen Diagnostics, Cache DNA, Concerto Biosciences, Stately Bio, Ramona Optics, Bifrost Biosystems, and Amber Bio. His laboratory has received research funding from Calico Life Sciences, Merck, and Genentech for unrelated work. None of these interests are connected to this study. The remaining authors declare no competing interests.

13. Factors associated with deaths by tuberculosis in the state of Mato Grosso, 2011-2020: retrospective cohort study.

Epidemiol Serv Saude. 2024 Nov 11;33:e20231402. doi: 10.1590/S2237-96222024V33E20231402.EN. eCollection 2024.

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OBJECTIVE: To investigate factors associated with tuberculosis deaths in Mato Grosso state, Brazil, from 2011 to 2020.
METHODS: Retrospective cohort study with data obtained from the Notifiable Health Conditions Information System and the Mortality Information System. Deaths were qualified using probabilistic linkage and analyzed using Poisson regression.
RESULTS: 12,331 cases and 525 deaths were identified over 10 years. The factors associated with death were: age ≥60 years (RR: 7.70; 95%CI 1.91;31.04), incomplete elementary and high school education (RR: 3.66; 95%CI 1.34;9.96), illiteracy (RR: 4.50; 95%CI 1.60;12.66), homeless population (RR: 2.41; 95%CI 1.34;4.35), alcohol use (RR: 1.45; 95%CI 1.04;2.02), male sex (RR: 1.48; 95%CI 1.04;2.09) and tobacco use (RR: 1.32; 95%CI 0.98;1.77). Laboratory confirmation was a protective factor.
CONCLUSION: Risk of death was higher in men over 60 years old, with low education levels, in vulnerable situations, and who used alcohol/tobacco.

Plain Language Summary: MAIN RESULTS: Risk of death was higher in the elderly, males, people with low education levels, homeless people, alcohol and tobacco users. Laboratory confirmation was a protective factor.
IMPLICATIONS FOR SERVICES: Raising awareness of health professionals regarding risk factors, especially regarding risk behaviors and laboratory confirmation of tuberculosis, to which efforts should be targeted.
PERSPECTIVES: It would be strategic to study survival in order to assimilate the effect of time and to study people with drug-resistant tuberculosis in order to update treatment recommendations. Health service managers need to define public policies aimed at the determinants found.

OBJETIVO: Investigar los factores asociados a la mortalidad por tuberculosis en Mato Grosso, entre 2011/2020.
MÉTODOS: Cohorte retrospectivo con datos obtenidos del Sistema de Información de Enfermedades de Declaración Obligatoria y Sistema de Información de Mortalidad. Las muertes se calificaron mediante relación probabilística y se analizaron por regresión de Poisson.
RESULTADOS: En 10 años se identificaron 12.331 casos y 525 muertes. Los factores asociados a muertes fueron: edad ≥ 60 años (RR: 7,70; IC95% 1,91;31,04), educación primaria/secundaria incompleta (RR: 3,66; IC95% 1,34;9,96), analfabetismo (RR: 4. 50 IC95% 1.60;12.66), población sin hogar (RR: 2.41; IC95% 1.34;4.35), alcohol (RR: 1.45; IC95% 1.04;2.02), sexo masculino (RR: 1.48; IC95% 1.04 ;2,09), tabaco (RR: 1,32; IC95% 0,98;1,77). La confirmación de laboratorio fue un factor protector (RR: 0,68; IC95% 0,52;0,93).

CONCLUSIÓN: Hubo mayor riesgo de muerte en hombres mayores de 60 años, con baja escolaridad, en situación de vulnerabilidad, que consumen alcohol/tabaco.

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PMID: 39536188 [Indexed for MEDLINE]

Conflict of interest statement: CONFLICTS OF INTEREST: The authors have no conflicts of interest to declare.

14. A CT-based radiomics analyses for differentiating drug-resistant and drug-sensitive pulmonary tuberculosis.

BMC Med Imaging. 2024 Nov 12;24(1):307. doi: 10.1186/s12880-024-01481-4.

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BACKGROUND: To explore the value of computed tomography based radiomics in the differential diagnosis of drug-sensitive and drug-resistant pulmonary tuberculosis.
METHODS: The clinical and computed tomography image data of 177 patients who were diagnosed with pulmonary tuberculosis through sputum culture and completed drug-susceptibility testing from April 2018 to December 2020 at the Second Hospital of Nanjing were retrospectively analyzed. Patients with drug-resistant pulmonary tuberculosis (n = 78) and drug-sensitive pulmonary tuberculosis (n = 99) were randomly divided into a training set (n = 124) and a validation set (n = 53) at a ratio of 7:3. Regions of interest were drawn to delineate the lesions and radiomics features were extracted from non-contrast computed tomography images. A radiomics signature based on the valuable radiomics features was constructed and a radiomics score was calculated. Demographic data, clinical symptoms, laboratory results and computed tomography imaging characteristics were evaluated to establish a clinical model. Combined with the Rad-score and clinical factors, a radiomics-clinical model nomogram was constructed.
RESULTS: Thirteen features were used to construct the radiomics signature. The radiomics signature showed good discrimination in the training set (area under

the curve (AUC), 0.891; 95% confidence interval (CI), 0.832-0.951) and the validation set (AUC, 0.803; 95% CI, 0.674-0.932). In the clinical model, the AUC of the training set was 0.780(95% CI, 0.700-0.859), while the AUC of the validation set was 0.692 (95% CI, 0.546-0.839). The radiomics-clinical model showed good calibration and discrimination in the training set (AUC, 0.932;95% CI, 0.888-0.977) and the validation set (AUC, 0.841; 95% CI, 0.719-0.962). CONCLUSIONS: Simple radiomics signature is of great value in differentiating drug-sensitive and drug-resistant pulmonary tuberculosis patients. The radiomics-clinical model nomogram showed good predictive, which may help clinicians formulate precise treatments.

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PMID: 39533228 [Indexed for MEDLINE]

Conflict of interest statement: Declarations Ethics approval and consent to participate The ethics committee of The Second Hospital of Nanjing (No. 2023-LY-kt106). approved this retrospective study with a waiver of informed consent because the study was an observational, retrospective study using a database from which the patients' identifying information had been removed. Consent for publication Not applicable. Competing interests The authors declare no competing interests.

15. Development and preliminary assessment of the iFIND TBR: all-in- one molecular diagnostic assay for rapid detection of Mycobacterium tuberculosis and rifampicin resistance.

Front Cell Infect Microbiol. 2024 Oct 29;14:1439099. doi: 10.3389/fcimb.2024.1439099. eCollection 2024.

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INTRODUCTION: Early and accurate diagnosis of tuberculosis (TB) is crucial for initiating timely treatment and preventing new infections. In this study, we introduced the iFIND TBR assay, an automated all-in-one tuberculosis detection approach that simultaneously detect Mycobacterium tuberculosis (MTB) and rifampicin (RIF) resistance.
METHODS: The limits of detection (LOD), sensitivity, specificity, and RIF-R rpoB mutation detection of the iFIND TBR were tested on Mycobacterium tuberculosis DNA or sputum samples spiked with known numbers of M.tuberculosis H37Rv. Frozen clinical samples from patients suspected of having TB were also tested.
RESULTS: The LOD of the iFIND TBR for MTB detection were 13.34 CFU/ml (95% CI, 11.71-16.47), and for RIF resistance was 109.79CFU/mL (95% CI, 95-138.19). The iFIND TBR assay accurately distinguish MTB strains from non-tuberculous mycobacteria (NTM) without any cross reactivity. Testing on 157 clinical sputum samples, compared with the bacteriologically TB standard, the overall sensitivity and specificity of the iFIND TBR was 100% (95%CI, 94.64, 100) and 85.29% (95% CI, 74.61, 92.72), respectively. When assessing RIF susceptibility, the iFIND TBR achieved a sensitivity of 98.15% (95% CI, 90.11-99.95) and a specificity of 85.71% (95% CI, 67.33-95.97), compared with phenotypic drug susceptibility testing. Discordant RIF susceptibility results were more frequently observed in samples exhibiting heteroresistance.
DISCUSSION: These findings demonstrate that iFIND TBR assay performs well in detecting TB and RIF resistance, and shows promise as a point-of-care tool in resource-limited areas.

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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.

16. Evaluation of clinical, laboratory, radiographical and histopathological characteristics in patients with spinal tuberculosis in the context of HIV infection: An analysis of 52 patients from a South African tertiary hospital.

S Afr Med J. 2024 Nov 4;114(11):e2065. doi: 10.7196/SAMJ.2024.v114i11.2065.

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BACKGROUND: South Africa (SA) has the highest prevalence of people with tuberculosis (TB) and HIV coinfection globally. People living with HIV have an increased risk of TB infection, and are more likely to develop extrapulmonary TB. Approximately 10 - 20% of extrapulmonary TB accounts for skeletal TB, with spinal involvement in 50 - 60% of instances. Previous studies have shown highly heterogenic results regarding the effect of HIV status on clinical and laboratory characteristics in patients with spinal TB (STB).
OBJECTIVE: To describe the clinical, laboratory, radiographical and histopathological characteristics of patients diagnosed with STB stratified by HIV status.
METHODS: Data from patients who were treated for STB at the Division of Orthopaedic Surgery, Groote Schuur Hospital, SA, between 2013 and 2016 were analysed. We compared clinical, laboratory, radiographical and histopathological parameters of STB patients with HIV infection to those without HIV infection. To assess differences in means between the two groups, an independent samples t-test was used for normally distributed continuous data, and a $\chi 2$ test for categorical data. To assess correlations between continuous data groups, the Pearson correlation coefficient was used.
RESULTS: We assessed 52 patients with STB (mean (standard deviation (SD) age 38 (15.2) years, range 17 - 80 years), of whom 55.8% were female, and 59.6% HIV infected. Five (9.6%) patients were identified with multidrug-resistant TB of the spine, with four (19.0%) in the HIV-infected cohort and one in the HIV-uninfected cohort (p=0.058). Significantly more STB patients without HIV infection presented with neurogenic symptoms (29%, p=0.029). The mean (SD) overall erythrocyte sedimentation rate was 69.3 (35.9) mm/h, with no significant difference between HIV-infected and HIV-uninfected patients (p=0.086). The rate of vertebral collapse was higher in the HIV-infected cohort (39% v. 67%, p=0.048). HIV-infected patients showed a higher count of involved vertebrae (mean 3.0 v. 3.85; p=0.034). There was no correlation between CD4 count and the

number of involved vertebrae. The mean (SD) number of granulomata per low-power field was 10 (12.6), with no difference between the two cohorts. However, we found a positive correlation between granuloma count and CD4 cell count in HIV-infected STB patients (Pearson 0.503, p=0.02), with significantly higher formation of granulomata at a CD4 cell count >400 cells/μL (p=0.045). CONCLUSION: In our cohort, HIV-infected patients with STB were more likely to present with vertebral collapse, and more vertebrae on average were diseased compared with HIV-uninfected patients with STB. CD4 cell count may affect granuloma formation, and it seems that HIV infection has a negative effect on cellular immunoresponse in STB, which emphasises the need for early antiretroviral therapy initiation.

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17. Leveraging large-scale Mycobacterium tuberculosis whole genome sequence data to characterise drug-resistant mutations using machine learning and statistical approaches.

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Tuberculosis disease (TB), caused by Mycobacterium tuberculosis (Mtb), is a major global public health problem, resulting in > 1 million deaths each year. Drug resistance (DR), including the multi-drug form (MDR-TB), is challenging control of the disease. Whilst many DR mutations in the Mtb genome are known, analysis of large datasets generated using whole genome sequencing (WGS) platforms can reveal new variants through the assessment of genotype-phenotype associations. Here, we apply tree-based ensemble methods to a dataset comprised of 35,777 Mtb WGS and phenotypic drug-susceptibility test data across first- and second-line drugs. We compare model performance across models trained using mutations in drug-specific regions and genome-wide variants, and find high predictive ability for both first-line (area under ROC curve (AUC); range

88.3-96.5) and second-line (AUC range 84.1-95.4) drugs. To aggregate information from low-frequency variants, we pool mutations by functional impact and observe large improvements in predictive accuracy (e.g., sensitivity: pyrazinamide + 25%; ethionamide + 10%). We further characterise loss-of-function mutations observed in resistant phenotypes, uncovering putative markers of resistance (e.g., ndh 293dupG, Rv3861 78delC). Finally, we profile the distribution of known DR-associated single nucleotide polymorphisms across discretised minimum inhibitory concentration (MIC) data generated from phenotypic testing (n = 12,066), and identify mutations associated with highly resistant phenotypes (e.g., inhA - 779G > T and 62T > C). Overall, our work demonstrates that applying machine learning to large-scale WGS data is useful for providing insights into predicting Mtb binary drug resistance and MIC phenotypes, thereby potentially assisting diagnosis and treatment decision-making for infection control.

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PMID: 39511309 [Indexed for MEDLINE]

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

18. Association between toxin-antitoxin system mutations and global transmission of MDR-TB.

BMC Infect Dis. 2024 Nov 5;24(1):1250. doi: 10.1186/s12879-024-10142-4.

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BACKGROUND: The emergence of Multidrug-Resistant Tuberculosis (MDR-TB) poses a significant threat to global tuberculosis control efforts. This study aimed to examine the influence of mutations in Toxin-Antitoxin system genes on the global transmission of MDR-TB caused by Mycobacterium tuberculosis (M. tuberculosis).
METHODS: Whole-genome sequencing was conducted on 13,518 M. tuberculosis isolates. Genes of the Toxin-Antitoxin system were obtained from the National Center for Biotechnology Information (NCBI) Gene database. Techniques such as Random Forest, Gradient Boosting Decision Tree, and Generalized Linear Mixed Models were employed to identify mutation sites in Toxin-Antitoxin system-related genes that facilitated the transmission of MDR-TB.
RESULTS: 4,066 (30.08%) were identified as MDR-TB strains of all analyzed isolates. We found significant associations between specific gene mutations and MDR-TB transmission clusters including mutations in Rv0298 (G213A), Rv1959c (parE1, C88T), Rv1960c (parD1, C134T), Rv1991A (maze, G156A), Rv2547 (vapB, C54G), Rv2862A (vapB23, T2C), and Rv3385c (vapB46, G70A). Additionally, several gene mutations associated with MDR-TB transmission clades such as Rv1956 (higA, G445T), Rv1960c (parD1, C134T), and Rv1962A (vapB35, G99A) were noted. Certain gene mutations including vapB35 (G99A), higA (G445T), and parD1 (C134T) correlated with cross-regional transmission clades.
CONCLUSION: This study highlights the significant association between specific gene mutations in the Toxin-Antitoxin system and the global transmission of MDR-TB, providing valuable insights for developing targeted interventions to control MDR-TB.

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19. Dynamic modelling of improved diagnostic testing for drug-resistant tuberculosis in high burden settings.

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BACKGROUND: Limited diagnostic testing for drug-resistant TB (DR-TB) may lead to high rates of misdiagnosis and undertreatment. Current diagnostic tests focus only on detection of rifampicin-resistant TB (RR-TB). This study aims to determine the impact of improved diagnostic testing for a wider range of drug resistance on DR-TB outcomes in high-burden TB settings, using the Philippines and Thailand as case studies.
METHODS: A dynamic compartmental model was designed to simulate population level TB transmission, accounting for acquired drug resistance from treatment failure of drug susceptible TB. Three scenarios were analyzed: (1) Use of GeneXpert MTB/RIF on all presumptive TB cases (Status Quo); (2) GeneXpert MTB/RIF + GeneXpert XDR, (3) GeneXpert MTB/RIF + targeted Next Generation Sequencing (tNGS). Scenarios were modelled over a 10-year period, from 2025 to 2034.
RESULTS: Compared to the status quo, Scenario 2 results in a fourfold increase in annual DR-TB cases diagnosed in the Philippines and a fivefold increase in Thailand. DR-TB treatment failure decreases by 20% in the Philippines and 23% in Thailand. Scenario 3 further increases DR-TB case detection, reducing DR-TB treatment failure by 26% in the Philippines and 29% in Thailand. Reductions in DR-TB incidence and mortality ranged from 3 to 6%.
CONCLUSION: The use of GeneXpert XDR or tNGS as an additional diagnostic test for DR-TB significantly improves DR-TB case detection and reduces treatment failure, supporting their consideration for use in high burden settings. These findings highlight the importance of detecting a wider range of TB resistance in addition to RR-TB, the potential impact these improved diagnostic tests can have on DR-TB outcomes, and the need for additional research on cost-effectiveness of these interventions.

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20. Cryo-EM structure of the Mycobacterium smegmatis MmpL5-AcpM complex.

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Mycobacterium tuberculosis, the causative agent of the airborne infection tuberculosis (TB), contains 13 mycobacterial membrane protein large (MmpL) transporters that can be divided into two distinct subclasses. These MmpL proteins play important functional roles within the mycobacterium and subsequently are considered attractive drug targets to combat TB infection. Previously, we reported both X-ray and cryo-electron microscopy (cryo-EM) structures of the MmpL3 transporter, providing high-resolution structural information for this subclass of the MmpL proteins. Thus far, there is no structural information available for the other subclass, which includes MmpL5, an inner membrane transporter that plays a critical role in iron hemostasis. Here, we report the first cryo-EM structure of the Mycobacterium smegmatis MmpL5 transporter bound with the meromycolate extension acyl carrier protein M (AcpM) to a resolution of 2.81 Å. Our structural data reveals that MmpL5 and AcpM interact in the cytoplasm to form a complex, and this allows us to propose that MmpL5 may also associate with the mycobactin L (MbtL) protein in a similar fashion to form a heterocomplex important for iron acquisition, which enables the survival and replication of the mycobacterium.
IMPORTANCE: The emergence and spread of multidrug-resistant tuberculosis (TB) present enormous challenges to the global public health. The causative agent, Mycobacterium tuberculosis, has now infected more than one-third of the world's population. Here, we report the first structure of the mycobacterial membrane protein large 5 (MmpL5), an essential transporter for iron acquisition, bound with the meromycolate extension acyl carrier protein M (AcpM), indicating a plausible pathway for mycobactin translocation. Our studies will ultimately inform an era in structure-guided drug design to combat TB infection.

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21. The CRISPR-dCas9 interference system suppresses inhA gene expression in Mycobacterium smegmatis.

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CRISPR-dead Cas9 interference (CRISPRi) has become a valuable tool for precise gene regulation. In this study, CRISPRi was designed to target the inhA gene of Mycobacterium smegmatis (Msm), a gene necessary for mycolic acid synthesis. Our findings revealed that sgRNA2 induced with 100 ng/ml aTc achieved over 90% downregulation of inhA gene expression and inhibited bacterial viability by approximately 1,000-fold. Furthermore, CRISPRi enhanced the susceptibility of M. smegmatis to isoniazid and rifampicin, which are both 50% and 90% lower than those of the wild-type strain or other strains, respectively. This study highlights the ability of CRISPRi to silence the inhA gene, which impacts bacterial viability and drug susceptibility. The findings provide valuable insights into the utility of CRISPRi as an alternative tool for gene regulation. CRISPRi might be further assessed for its synergistic effect with current anti-tuberculosis drugs and its possible implications for combating mycobacterial infections, especially drug-resistant tuberculosis.

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22. Toxoplasma gondii macrophage migration inhibitory factor shows anti-Mycobacterium tuberculosis potential via AZIN1/STAT1 interaction.

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Mycobacterium tuberculosis (MTB) is a pathogenic bacterium, belonging to the family Mycobacteriaceae, that causes tuberculosis (TB). Toxoplasma gondii macrophage migration inhibitory factor (TgMIF), a protein homolog of macrophage migration inhibitory factor, has been explored for its potential to modulate immune responses during MTB infections. We observed that TgMIF that interacts with CD74, antizyme inhibitor 1 (AZIN1), and signal transducer and activator of transcription 1 (STAT1) modulates endocytosis, restoration of mitochondrial function, and macrophage polarization, respectively. These interactions promote therapeutic efficacy in mice infected with MTB, thereby presenting a potential route to host-directed therapy development. Furthermore, TgMIF, in combination with first-line TB drugs, significantly inhibited drug-resistant MTB strains, including multidrug-resistant TB. These results demonstrate that TgMIF is potentially a multifaceted therapeutic agent against TB, acting through immune modulation, enhancement of mitochondrial function, and dependent on STAT1 and AZIN1 pathways.

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23. Frameshift mutations in the mmpR5 gene can have a bedaquiline-susceptible phenotype by retaining a protein structure and function similar to wild-type Mycobacterium tuberculosis.

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Bedaquiline (BDQ) is crucial for the treatment of rifampicin-resistant tuberculosis, yet resistance threatens its effectiveness, mainly linked to mutations in the mmpR5 (Rv0678) gene. While frameshift mutations are thought to produce non-functional proteins, we hypothesize that they can result in conserved proteins through late-stop codons or alternative reading frames and remain BDQ susceptible. We extracted 512 isolates harboring frameshift mutations in mmpR5 from the World Health Organization (WHO) catalog and 68 isolates with minimum inhibitory concentration (MIC) in mycobacterial growth indicator tube (MGIT) through a literature review. Using BioPython and AlphaFold2 we computed open (ORF) and alternative reading frames (ARFs) sequences and protein structures and assessed similarity to the wild type using an alignment and template modeling (TM)-score. Among the WHO 512 isolates, 24.8% were BDQ-sensitive. Out of 184 unique frameshift mutations with available nucleotide information, a late-stop codon in the ORF occurred for 32% of the mutations. Also, 40.7% resulted in a conserved sequence, through the ORF or one of the forward ARFs. In 68 isolates with available MGIT MIC data, the presence of late-stop codons in the ORF (OR 4.71, 95% CI 1.36-19.3) or a conserved reading frame (OR 10.4, 95% CI 2.07-102.9) were associated with BDQ sensitivity. Protein structures from the conserved sequences showed high similarity (TM > 0.8). We show that frameshift mutations may retain BDQ susceptibility through late-stop codons in the ORF or conserved ARFs. These findings could improve the prediction of the BDQ phenotype from genomic data and have important implications for treatment decisions. Research Foundation-Flanders, Academy of Medical Sciences, the Wellcome Trust, the Government Department of Business, Energy and Industrial Strategy, the British Heart Foundation and Diabetes UK, and the Global Challenges Research Fund.IMPORTANCETuberculosis (TB), caused by Mycobacterium tuberculosis, remains the deadliest infectious disease and is particularly challenging to treat when it becomes drug-resistant. Bedaquiline (BDQ) is a recently recommended core drug for treating drug-resistant TB. However, resistance to bedaquiline is already emerging, primarily due to mutations in the mmpR5 gene. Identifying which mutations cause resistance and which do not is a critical knowledge gap. In particular, little is known about the effect of frameshift mutations, typically thought to make TB bacteria resistant to bedaquiline by producing non-functional proteins. Yet, one-quarter of isolates with a frameshift mutation are still susceptible to bedaquiline. How the bacteria produce a functional protein despite the frameshift mutation is unknown. We analyzed over 500 frameshift mutations using computational methods

to model their effects on protein structure and bedaquiline resistance. Our findings revealed that some frameshift mutations can still produce functional proteins, allowing bacteria to remain sensitive to bedaquiline. Specifically, bacteria can produce a functional protein despite frameshift mutations if the mutation occurs near the end of the protein or if an alternative reading frame is available. These insights improve our ability to interpret mutations associated with bedaquiline, the most important drug for drug-resistant TB, allowing more accurate and effective treatment decisions.

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24. Multidrug-resistant tuberculosis treatment outcomes and associated factors at Yirgalem General Hospital, Sidama Region, South Ethiopia: a retrospective cohort study.

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BACKGROUND: The spread of multidrug-resistant tuberculosis (MDR-TB) poses a significant challenge to TB control efforts. This study evaluated the treatment outcomes and associated factors among patients receiving treatment for MDR-TB in southern Ethiopia.
METHODS: A retrospective follow-up study covering ten years, from 2014 to 2023, analyzed the records of confirmed cases of pulmonary TB admitted to Yirgalem General Hospital, an MDR-TB treatment initiation center in the Sidama Region. To compare the successful treatment outcomes across the years, a chi-square test of independence was conducted. Bivariate and multivariable logistic regression models were used to identify factors associated with treatment outcomes for MDR-TB.
RESULTS: Out of 276 confirmed MDR-TB cases, 4(1.4%) were diagnosed with resistance to second-line drugs (SLDs). Overall, 138 patients achieved favourable treatment outcomes, resulting in a treatment success rate of 50.0% [95% CI 44.1-55.9%]. Among these 138 patients, 105(76.1%, 95 CI 68.7-83.5%) were cured, while 33(23.9%, 95 CI 16.5-31.3%) completed their treatment. The

successful treatment outcomes varied significantly across the years, ranging from 3.6% in 2020 to 90% in 2021. The analysis indicated a statistically significant difference in treatment outcomes when considering data from 2014 to 2023 ($\chi 2 = 44.539$, $p = 0.001$). The proportion of patients with deaths, lost-to-follow-up (LTFU), treatment failures and not evaluated were 7.9% [95% CI 4.8-11.2%], 10.9% [95% CI 7.2-14.6%), 2.2% [95% CI 1.1-3.3%), and 28.9% [95% CI 23.7-34.2%] respectively. Individuals with a positive HIV status had significantly lower odds of a favorable treatment outcome [AOR = 0.628, 95% CI (0.479-0.824), $p = 0.018$]. Similarly, patients with a BMI of less than 18 are more likely to have unfavorable treatment outcomes compared to those with a BMI of 18 or higher [AOR = 2.353, 95% CI 1.404-3.942, $p < 0.001$].
CONCLUSION: The study revealed a concerning 1.4% prevalence of additional resistance to SLDs. The 50% rate of unfavorable treatment among MDR-TB cases exceeds the target set by the WHO. A significant number of patients (10.9%) were LTFU, and the 28.9% categorized as 'not evaluated' is also concerning. Enhanced strategic interventions are needed to reduce such cases, and factors associated with poor treatment outcomes should receive greater attention. Future prospective studies can further explore the factors influencing improved treatment success.

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25. A novel dual probe-based method for mutation detection using isothermal amplification.

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Cost efficient and rapid detection tools to detect mutations especially those linked to drug-resistance are important to address concerns of the rising multi-drug resistance infections. Here we integrated dual probes, namely a calibrator probe and an indicator probe, into isothermal amplification detection system. These two probes are designed to bind distinct regions on the same amplicon to determine the presence or absence of mutation. The calibrator probe signal is used as an internal signal calibrator for indicator probe which

detects the presence or absence of the mutation. As an illustrative example, we evaluated the applicability of this dual probe method for detecting mutations associated with rifampicin (RIF) drug resistance at codons 516, 526 and 531 of the rpoB gene in Mycobacterium tuberculosis. In this assessment, we examined 127 artificial samples comprising wild types and mutants with single or multiple mutations. Our results demonstrated 100% accuracy for both wild types and mutants for mutations at codons 526 and 531. As regards to mutations at codon 516, the wild type was identified with 100% accuracy, while the mutants were identified with 95% accuracy. Moreover, when we extended our evaluation to include clinical MTB strains and the Zeptometrix MTB Verification panel, our method achieved 100% accuracy (5 out of 5) in identifying wild-type strains. Additionally, we successfully detected a RIF-resistant strain with mutations at codon 531 of the rpoB gene in Zeptometrix verification panel. Our isothermal mutation detection system, relying on dual probes exhibits a versatile approach. With the capability to identify mutations without prior knowledge of their specific mutation direction, our dual-probe method shows significant promise for applications in drug resistance nucleic acid testing, particularly in resource-limited settings.

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26. The rising tide of tuberculosis in Pakistan: Factors, impact, and multi-faceted approaches for prevention and control.

Health Sci Rep. 2024 Oct 20;7(10):e70130. doi: 10.1002/hsr2.70130. eCollection 2024 Oct.

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BACKGROUND: Tuberculosis (TB) remains a major public health concern in Pakistan, which is ranked fifth among high-burden TB nations worldwide. The growing frequency of drug-resistant TB strains, particularly multidrug-resistant TB (MDR-TB), creates new obstacles. Socioeconomic factors, a lack of awareness, and inadequate healthcare infrastructure all contribute to the spread of the disease.
OBJECTIVE: This study investigates the mechanisms contributing to the growth in tuberculosis cases in Pakistan, the implications for public health, and multifaceted approaches to prevention and control.
METHODS: A comprehensive literature study was undertaken, including an analysis of peer-reviewed articles, World Health Organization (WHO) data, and government sources, to identify factors driving tuberculosis prevalence, control issues, and disease-fighting tactics.Result: Several factors like Poverty, overcrowding, malnutrition, stigma, and restricted access to healthcare services are all factors contributing to an increase in tuberculosis incidence in Pakistan. The prevalence of MDR-TB, along with a lack of an integrated healthcare response, complicates efforts to contain the disease's spread. Tuberculosis has a profound social, mental, and financial impact on individuals and communities. Public health efforts, such as the National Tuberculosis Control Program (NTP) and international partnerships, have been created to eradicate tuberculosis, although considerable hurdles persist.
OBJECTIVE: This study investigates the mechanisms contributing to the growth in tuberculosis cases in Pakistan, the implications for public health, and multifaceted approaches to prevention and control.

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27. Patient and provider costs of the new BPaL regimen for drug-resistant tuberculosis treatment in South Africa: A cost-effectiveness analysis.

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BACKGROUND: Drug-resistant (DR) tuberculosis (TB) is typically characterized by resistance to a single or combination of first- and/or second-line anti-TB agents and commonly includes rifampicin-resistant (RR)-TB, multidrug-resistant (MDR)-TB, pre-extensively drug-resistant (pre-XDR)-TB and XDR-TB. Historically, all variations of DR-TB required treatment with second-line drugs which are less effective and more toxic than first-line options, have a longer treatment duration and are more expensive to both patients and providers. The World Health Organization (WHO) now recommends a new second-line 3-drug 6-month all-oral regimen consisting of bedaquiline, pretomanid, and linezolid referred to as BPaL. We estimate patient and provider costs of DR-TB treatment with BPaL compared to the current standard of care in South Africa.
METHODS AND FINDINGS: In coordination with South Africa's BPaL clinical access programme (CAP) we conducted an economic evaluation of A) patient costs through a cross-sectional patient cost survey and B) provider costs through a bottom-up costing analysis consisting of a retrospective medical record review (patient resource-use) and top-down financial record review (fixed/shared costs such as overhead). Across both costing perspectives, we compare costs of 1) BPaL, to current standard of care options including the 2) 9-11-month standard short oral regimen (SSOR) and 3) 18-21-month standard long oral regimen (SLOR). Eligible patients included those ≥14 years old with confirmed sputum pulmonary RR/MDR-TB, pre-XDR or XDR-TB. All costs are reported in 2022 United States Dollar (US$). A total of 72 patients were enrolled and completed the patient cost survey (41.7% on BPaL, 16.7% on the SSOR and 41.7% on the SLOR). Mean on-treatment patient costs were lowest among those on BPaL ($56.6) and increased four-fold among those on the SSOR ($228.1) and SLOR ($224.7). Direct medical patient costs were negligible across all treatment regimens, while direct non-medical patient and guardian costs for travel, food and nutritional supplementation accounted for the largest proportion of total costs ($54.6, $227.8 and $224.3 for BPaL, the SSOR and SLOR respectively). In assessing provider costs, a total of 112 medical records were reviewed (37.5%, 41.1% and 21.4% on BPaL, the SSOR and SLOR respectively). Total provider costs for producing a favorable treatment outcome (cured/completed treatment) were similar among those on BPaL ($4,948.7 per patient) and the SSOR ($4,905.6 per patient) with costs increasing substantially

among those on the SLOR ($8,919.9 per patient). Based on incremental cost-effectiveness ratios (ICERs), at even the lowest willingness to pay (WTP) threshold, treatment with the new BPaL regimen was more cost-effective than current standard of care treatment options (ICER: $311.4 < WTP: $3,341). CONCLUSIONS: When using the newly recommended BPaL regimen, cost to patients decreased by 75% compared to current standard of care treatment options in South Africa. Due in part to higher resource-use within the BPaL CAP offsetting the shorter treatment duration, cost of treatment provision through BPaL and the 9-11-month SSOR were similar. However, when considering cost and treatment outcomes, BPaL was more cost-effective than other standard of care regimens currently available for DR-TB in South Africa.

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28. Draft genome sequence of Mycolicibacterium conceptionense isolated from the sputum sample of a patient with pulmonary tuberculosis.

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We report the draft genome of Mycolicibacterium conceptionense, a rapidly growing nontuberculous mycobacterium, isolated from the sputum sample of a patient undergoing treatment for multidrug-resistant tuberculosis in Delhi, India. The 6,366,717-bp genome contains 6,124 coding sequences, one 5S rRNA, three 16S rRNAs, six 23S rRNAs, and 49 tRNAs.

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PMID: 39422493

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29. Impact of isoniazid monoresistance on overall and vulnerable patient populations in Taiwan.

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Isoniazid is an early bactericidal anti-tuberculosis (TB) agent and isoniazid mono-resistance TB is the most prevalent drug-resistant TB worldwide. Concerns exist regarding whether resistance to isoniazid would lead to delayed culture conversion and worst outcomes. From January 2008 to November 2017, adult culture-positive pulmonary TB patients receiving isoniazid, rifampicin, pyrazinamide, and ethambutol were identified through Taiwan Center for Disease Control database and were followed until the end of 2017. Primary outcomes included time to sputum culture conversion (SCC) within two months. Secondary outcomes included death and unfavourable outcomes at the end of 2nd month. A total of 37,193 drug-susceptible and 2,832 isoniazid monoresistant pulmonary TB

patients were identified. Compared with no resistance, isoniazid monoresistance was not associated with a delayed SCC (HR: 0.99, 95% CI: 0.94─1.05, p = 0.8145), a higher risk of 2-month mortality (HR: 1.19, 95% CI: 0.92─1.53, p = 0.1884), and unfavourable outcomes at 2nd month (OR: 1.05, 95% CI: 0.97─1.14, p = 0.2427). Isoniazid monoresistance was associated with delayed SCC (HR: 0.90, 95% CI: 0.83─0.98, p = 0.0099) and a higher risk of unfavourable outcomes (OR:1.18, 95% CI: 1.05─1.32, p = 0.0053) in patients aged between 20 and 65, and delayed SCC in patients without underlying comorbidities (HR: 0.90, 95% CI: 0.81─0.98, p = 0.0237). Isoniazid mono-resistant TB had a comparable outcome with drug-susceptible TB at the end of the intensive phase. Healthy, and non-elderly patients were more likely to had culture persistence, raising concerns about disease transmission in these subgroups and warranting early molecular testing for isoniazid resistance.

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30. Widespread loss-of-function mutations implicating preexisting resistance to new or repurposed anti-tuberculosis drugs.

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BACKGROUND: Five New or Repurposed Drugs (NRDs) were approved in the last decade for treatment of multi-drug resistant tuberculosis: bedaquiline, clofazimine, linezolid, delamanid, and pretomanid. Unfortunately, resistance to these drugs emerged faster than anticipated, potentially due to preexisting resistance in naïve strains. Previous investigations into the rapid emergence have mostly included short variants. For the first time, we utilize de novo-assembled genomes, and systematically include Structural Variations (SV) and heterogeneity to comprehensively study this rapid emergence. We show high prevalence of preexisting resistance, identify novel markers of resistance, and lay the

foundation for preventing preexisting resistance in future drug development.
METHODS: First, a systematic literature review revealed 313 NRD resistance variants in 13 genes. Next, 409 globally diverse clinical isolates collected prior to the drugs' programmatic use (308 were multidrug resistant, 106 had de novo assembled genomes) were utilized to study the 13 genes comprehensively for conventional, structural, and heterogeneous variants.
FINDINGS: We identified 5 previously reported and 67 novel putative NRD resistance variants. These variants were 2 promoter mutations (in 8/409 isolates), 13 frameshifts (21/409), 6 SVs (9/409), 35 heterogeneous frameshifts (32/409) and 11 heterogeneous SVs (12/106). Delamanid and pretomanid resistance mutations were most prevalent (48/409), while linezolid resistance mutations were least prevalent (8/409).
INTERPRETATION: Preexisting mutations implicated in resistance to at least one NRD was highly prevalent (85/409, 21 %). This was mostly caused by loss-of-function mutations in genes responsible for prodrug activation and efflux pump regulation. These preexisting mutations may have emerged through a bet-hedging strategy, or through cross-resistance with non-tuberculosis drugs such as metronidazole. Future drugs that could be resisted through loss-of-function in non-essential genes may suffer from preexisting resistance. The methods used here for comprehensive preexisting resistance assessment (especially SVs and heterogeneity) may mitigate this risk during early-stage drug development.

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31. Discovery of benzo[c]phenanthridine derivatives with potent activity against multidrug-resistant Mycobacterium tuberculosis.

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Mycobacterium tuberculosis (Mtb), the pathogen responsible for tuberculosis (TB), is the leading cause of bacterial disease-related death worldwide. Current antibiotic regimens for the treatment of TB remain dated and suffer from long treatment times as well as the development of drug resistance. As such, the search for novel chemical modalities that have selective or potent anti-Mtb properties remains an urgent priority, particularly against multidrug-resistant (MDR) Mtb strains. Herein, we design and synthesize 35 novel benzo[c]phenanthridine derivatives (BPDs). The two most potent compounds, BPD-6 and BPD-9, accumulated within the bacterial cell and exhibited strong inhibitory activity (MIC90 ~2 to 10 μM) against multiple Mycobacterium strains while remaining inactive against a range of other Gram-negative and Gram-positive bacteria. BPD-6 and BPD-9 were also effective in reducing Mtb survival within infected macrophages, and BPD-9 reduced the burden of Mycobacterium bovis BCG in the lungs of infected mice. The two BPD compounds displayed comparable efficacy to rifampicin (RIF) against non-replicating Mtb (NR-Mtb). Importantly, BPD-6 and BPD-9 inhibited the growth of multiple MDR Mtb clinical isolates. Generation of BPD-9-resistant mutants identified the involvement of the Mmr efflux pump as an indirect resistance mechanism. The unique specificity of BPDs to Mycobacterium spp. and their efficacy against MDR Mtb isolates suggest a potential novel mechanism of action. The discovery of BPDs provides novel chemical scaffolds for anti-TB drug discovery.IMPORTANCEThe emergence of drug-resistant tuberculosis (TB) is a serious global health threat. There remains an urgent need to discover new antibiotics with unique mechanisms of action that are effective against drug-resistant Mycobacterium tuberculosis (Mtb). This study shows that novel semi-synthetic compounds can be derived from natural compounds to produce potent activity against Mtb. Importantly, the identified compounds have narrow spectrum activity against Mycobacterium species, including clinical multidrug-resistant

(MDR) strains, are effective in infected macrophages and against non-replicating Mtb (NR-Mtb), and show anti-mycobacterial activity in mice. These new compounds provide promising chemical scaffolds to develop potent anti-Mtb drugs of the future.

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32. The catalogue of Mycobacterium tuberculosis mutations associated with drug resistance to 12 drugs in China from a nationwide survey: a genomic analysis.

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BACKGROUND: WHO issued the first edition catalogue of Mycobacterium tuberculosis complex (MTBC) mutations associated with drug resistance in 2021. However, country-specific issues might lead to arising complex and additional drug-resistant mutations. We aimed to fully reflect the characteristics of drug resistance mutations in China.
METHODS: We analysed MTBC isolates from the nationwide drug-resistant tuberculosis surveillance with 70 counties in 31 provinces, municipalities, and autonomous regions in China. Three types of MYCOTB plates were used to perform drug susceptibility testing for 12 antibiotics (rifampicin, isoniazid, ethambutol, levofloxacin, moxifloxacin, amikacin, kanamycin, ethionamide, clofazimine, linezolid, delamanid, and bedaquiline). Mutations were divided into five groups according to their odds ratios, positive predictive values, false discovery rate-corrected p values, and 95% CIs: (1) associated with resistance; (2) associated with resistance-interim; (3) uncertain significance; (4) not associated with resistance-interim; and (5) not associated with resistance. The Wilcoxon rank-sum and Kruskal-Wallis tests were used to quantify the association between mutations and minimum inhibitory concentrations (MICs). Our dataset was compared with the first edition of the WHO catalogue.
FINDINGS: We analysed 10 146 MTBC isolates, of which 9071 (89·4%) isolates were included in the final analysis. 744 (8·2%) isolates were resistant to rifampicin and 1339 (14·8%) to isoniazid. 208 (1·9%) of 11 065 mutations were classified as associated with resistance or associated with resistance-interim. 33 (97·1%) of 34 mutations in group 1 and 92 (52·9%) of 174 in group 2 also appeared in groups 1 or 2 of the WHO catalogue. Of 81 indel mutations in group 2, 15 (18·5%) were in the WHO catalogue. The newly discovered mutation gyrA_Ala288Asp was associated with levofloxacin resistance. MIC values for rifampicin, isoniazid, moxifloxacin, and levofloxacin corresponding to resistance mutations in group 1 were significantly different ($p<0·0001$), and 12 high-level resistance mutations were detected. 61 mutations in group 3 occurred as solo in at least five phenotypically susceptible isolates, but with MIC values moderately higher than other susceptible isolates. Among 945 phenotypically resistant but genotypically susceptible isolates, 433 (45·8%) were mutated for at least one efflux pump gene.
INTERPRETATION: Our analysis reflects the complexity of drug resistance mutations in China and suggests that indel mutations, efflux pump genes, protein structure, and MICs should be fully considered in the WHO catalogue, especially in countries with a high tuberculosis burden.
FUNDING: National Key Research and Development Program of China and the Science and Technology Major Project of Tibetan Autonomous Region of China.

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33. Transmission of multidrug-resistant tuberculosis in Jiangxi, China, and associated risk factors.

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In order to effectively combat the urgent threat of multidrug-resistant tuberculosis (MDR-TB), it is imperative to gain a comprehensive understanding of the drug-resistant profiles, transmission dynamics, and associated risk factors. Our study encompassed a population-based retrospective analysis with 130 MDR-TB patients from 2018 to 2021. The research methodology incorporated whole-genome sequencing, drug susceptibility testing , and logistic regression analysis to discern the risk factors of genomic clustering linked to recent transmission. The findings from phenotypic drug resistance assessments revealed notable resistance rates: ethambutol at 62.3% (81/130), streptomycin at 72.3% (94/130), levofloxacin at 51.5% (67/130), and moxifloxacin at 50.0% (65/130). Furthermore, among all patients, 38 individuals (29.23%, 38/130) were found to be part of 17 clusters, indicating instances of recent MDR-TB transmission. The genomic clustering patients were deeply investigated. Lineage 2.2.1 was established as the primary sub-lineage (86.15%, 112/130), followed by lineage 4 (9.23%, 12/130). Moreover, the logistic regression analysis underscored that unemployment, farming occupations, and prior TB treatment were identified as significant risk factors for recent transmission.
IMPORTANCE: The high prevalence of multidrug-resistant tuberculosis (MDR-TB) in Jiangxi Province highlights the importance of understanding the genetic background and drug resistance patterns of these strains. This knowledge is crucial for developing effective control methods. Furthermore, in light of the significance of preventing transmission among tuberculosis patients, whole-genome sequencing was utilized to investigate the recent transmission of MDR-TB and identify associated risk factors. The findings revealed that

individuals in the farming sector, those who are unemployed, and patients with a history of tuberculosis treatment are at elevated risk. Consequently, targeted public interventions for these at-risk groups are imperative.

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34. Contribution of direct InhA inhibitors to novel drug regimens in a mouse model of tuberculosis.

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Isoniazid is an important first-line medicine to treat tuberculosis (TB). Isoniazid resistance increases the risk of poor treatment outcomes and development of multidrug resistance, and is driven primarily by mutations involving katG, encoding the prodrug-activating enzyme, rather than its validated target, InhA. The chemical tractability of InhA has fostered efforts to discover direct inhibitors of InhA (DIIs). In this study, we bridge the gap in understanding the potential contribution of DIIs to novel combination regimens and demonstrate a clear distinction of DIIs, like GSK693 and the newly described GSK138, from isoniazid, based on activity against clinical isolates and contribution to novel drug regimens. The results suggest that DIIs, specifically GSK138 and GSK693, could be promising partners in novel drug regimens, including those used against isoniazid-resistant TB, potentially enhancing their efficacy and/or preventing the selection of resistant mutants and supporting the continued exploration of InhA as a promising target for TB drug development.

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35. Assessing hepatotoxicity in novel and standard short regimens for rifampicin-resistant tuberculosis: Insights from the TB-TRUST and TB-TRUST-plus trials.

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OBJECTIVES: Efforts to shorten rifampicin-resistant tuberculosis (RR-TB) treatment have led to concerns about hepatotoxicity in shorter regimens. We evaluated hepatotoxicity in two novel regimens against the standard shorter regimen recommended by the World Health Organization (WHO).
METHODS: Participants from the TB-TRUST and TB-TRUST plus trials were assigned to the WHO shorter regimen, a levofloxacin (Lfx)-based regimen, or a bedaquiline (Bdq)-based regimen. Liver function was tested bi-weekly in the first month,

then monthly until treatment ended. Eligibility required receiving at least one drug dose and undergoing at least two liver function tests.
RESULTS: Of 429 patients, hepatotoxicity was most prevalent in the WHO shorter group (26.7% of 169), compared to 4.7% in the Lfx group (172 patients), and 5.7% in the Bdq group (88 patients). The median peak alanine aminotransferase levels were 1.67 × upper limit of normal (ULN) for WHO, 0.82 × ULN for Lfx, and 0.88 × ULN for Bdq groups. The incidence of drug-induced liver injury was significantly higher in the WHO group (18.3%) than in the Lfx (3.5%) and Bdq (4.6%) groups. The time to significant alanine aminotransferase elevation was about 2.8 months, with no differences between groups.
CONCLUSIONS: Two novel regimens demonstrated lower hepatotoxicity compared to the WHO's shorter regimen. Entire course management monitoring is recommended in RR-TB treatment.

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36. Enhancing the therapeutic window for Spectinamide anti-tuberculosis Agents: Synthesis, Evaluation, and activation of phosphate prodrug 3408.

Bioorg Med Chem Lett. 2024 Nov 1;112:129934. doi: 10.1016/j.bmcl.2024.129934. Epub 2024 Aug 28.

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Spectinamides are a novel class of narrow-spectrum antitubercular agents with the potential to treat drug-resistant tuberculosis infections. Spectinamide 1810 has shown a good safety record following subcutaneous injection in mice or infusion in rats but exhibits transient acute toxicity following bolus administration in either species. To improve the therapeutic index of 1810, an injectable prodrug strategy was explored. The injectable phosphate prodrug 3408 has a superior maximum tolerated dose compared to 1810 or Gentamicin. Following intravenous administration in rodents, prodrug 3408 was quickly converted to 1810. The resulting 1810 exposure and pharmacokinetic profile after 3408 administration was identical to equivalent molar amounts of 1810 given directly by intravenous administration. 3408 and the parent 1810 exhibited similar overall efficacy in a BALB/c acute tuberculosis efficacy model. Delivery of 1810 in phosphate prodrug form, therefore, holds the potential to improve further the therapeutic index of an already promising tuberculosis antibiotic.

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PubMed Non-Open Access:

37. JIB-04, an inhibitor of Jumonji histone demethylase as a potent antitubercular agent against Mycobacterium tuberculosis.

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The increasing drug resistance of Mycobacterium tuberculosis (Mtb), coupled with the limited availability of effective anti-tuberculosis medications, poses significant challenges for the management and treatment of tuberculosis (TB). Globally, non-tuberculous mycobacteria (NTM) infections are increasing, with Mycobacterium avium complex and Mycobacterium abscessus (Mab) being the most common in labs and having few treatment options. There's an urgent need for innovative therapies against Mtb and NTM that are effective and have minimal side effects. The study evaluated the in vitro efficacy of JIB-04, a Jumonji histone demethylase inhibitor, against Mtb, Mab, and multidrug-resistant (MDR) clinical isolates using the minimum inhibitory concentration (MIC) assay. We also determined the minimum bactericidal concentrations (MBCs) of JIB-04 against the H37Rv and H37Ra strains. A time-kill assay was performed to assess the comparative efficacy of JIB-04 and rifampicin against H37Ra. Additionally, the study investigated the impact of JIB-04 on biofilm formation and the persistence of H37Ra over extended periods. Our findings demonstrated a substantial inhibitory effect of JIB-04 on the growth of Mab, Mtb, and MDR clinical isolates. JIB-04 showed bactericidal effects at twice the MIC, outperforming rifampicin in reducing viable cell counts over 8 days. It showed moderate cytotoxicity to mammalian cells but effectively inhibited biofilm formation. In our anoxia model, JIB-04 induced a significant, concentration-dependent reduction in bacterial load. JIB-04 is a promising candidate for the treatment of MDR tuberculosis.

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Conflict of interest statement: Declarations Conflict of interest The authors declare no competing interests. Ethics approval and consent to participate Not applicable.

38. [Analysis of the epidemic characteristics and treatment outcomes of rifampicin-resistant pulmonary tuberculosis in Yangzhou City from 2012 to 2020].

Zhonghua Yu Fang Yi Xue Za Zhi. 2024 Nov 6;58(11):1679-1683. doi: 10.3760/cma.j.cn112150-20240102-00003.

[Article in Chinese; Abstract available in Chinese from the publisher]

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Information on patients with rifampicin-resistant pulmonary tuberculosis (RR-PTB) in Yangzhou City from 2012 to 2020 was obtained from the Information System of the Chinese Center for Disease Control and Prevention. The epidemic characteristics of RR-PTB patients were analyzed by using χ2 test. The average annual registered incidence rate of RR-PTB patients in Yangzhou City from 2012 to 2020 was 0.57/100 000, and the difference between the registered incidence rates in each year was statistically significant (χ2=29.326, P<0.001). The proportion of re-treated patients (64.8%) was higher than that of newly treated patients (35.2%, χ2=50.593, P<0.001). The registered incidence rate in males (0.91/100 000) was higher than that in females (0.24/100 000, χ2=80.566, P<0.001). The age distribution showed that the highest incidence rate was in the age group≥60 years (0.96/100 000) and the lowest was in the age group 0-<45 years (0.31/100 000, χ2=55.853, P<0.001). From 2012 to 2020, Baoying County had the largest number of registered RR-PTB patients (44 cases), and its registered incidence rate (0.64/100 000) was only lower than that of Guangling District (0.98/100 000). The registered incidence rate of RR-PTB patients in Baoying County during 2016-2020 also increased significantly compared to 2012-2015 (P=0.001). Logistic regression was used to analyze the factors related to the treatment outcome of RR-PTB patients. The results showed that patients aged≥60 years and those classified as the re-treatment were risk factors for successful treatment of RR-PTB patients (P<0.05). In summary, males, people aged≥60 years, patients classified as the re-treatment, and residents of Baoying County should be the key populations for RR-PTB epidemic prevention and control in Yangzhou City.

Publisher:
从中国疾病预防控制信息系统中获取2012—2020年扬州市利福平耐药肺结核（RR-PTB）患者病例资料，采用χ2检验分析RR-PTB患者流行特征，结果显示，2012—2020年扬州市RR-PTB患者年均登记发病率0.57/10万，各年份登记发病率差异有统计学意义（χ

2=29.326，P<0.001），复治患者占比（64.8%）高于初治患者（35.2%，χ2=50.593，P<0.001）。男性登记发病率（0.91/10万）高于女性（0.24/10万，χ2=80.566，P<0.001）。年龄分布显示，患者登记发病率以≥60岁年龄段最高（0.96/10万），0~<45岁年龄段最低（0.31/10万，χ2=55.853，P<0.001）。2012—2020年宝应县RR-PTB患者登记数（44例）最多，登记发病率（0.64/10万）仅次于广陵区（0.98/10万），而2016—2020年与2012—2015年相比，宝应县RR-PTB患者登记发病率亦显著增加（P=0.001）。采用logistic回归分析RR-PTB患者的治疗转归相关因素，结果显示，患者年龄≥60岁和复治分类为影响RR-PTB患者成功治疗的危险因素（P<0.05）。综上，扬州市RR-PTB疫情防控的重点人群为男性、≥60岁人群、复治患者和宝应县地区的居民。.

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39. [Clinical application of targeted next generation sequencing in detecting rifampicin and rifabutin resistance in tuberculosis patients].

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To evaluate the clinical value of targeted next generation sequencing (tNGS) in diagnosing rifampicin and rifabutin resistance in tuberculosis patients. In this retrospective cohort study, 119 culture-positive Mycobacterium tuberculosis (MTB) strains from tuberculosis patients in Shenzhen Third People's Hospital from 2020 to 2023 were collected, then tNGS was performed to detect mutations of rpoB gene. Fourteen different types of rpoB gene mutation were detected in 46 mutation MTB strains, including 43 resistance related mutations and 3 synonymous mutations at codon 529. Using the phenotypic drug susceptibility results of rifampicin and rifabutin as the reference standard, the sensitivities of tNGS for detecting resistance to rifampicin and rifabutin were 100%, and the specificities were 96.2% and 89.4% respectively, therefore, tNGS showed good

diagnostic performance. Mutations at positions 531 and 526 of rpoB were highly associated with resistance to rifampicin and rifabutin. Moreover, the results of tNGS from the clinical specimens were consistent with those from the corresponding culture strains. tNGS analysis was performed on 83 MTB strains from 18 patients with multiple positive cultures. The results showed that 2 patients with no mutations in the initial MTB strains were subsequently detected with rpoB gene mutation and their phenotypic drug susceptibilities changed from sensitive to resistant. In summary, using tNGS to detect rpoB mutations can reduce false positive results caused by synonymous mutations, and have satisfactory performance for the diagnosis of rifampicin and rifabutin resistance. tNGS can directly detect clinical sputum samples, and also can be used to dynamically monitor the molecular resistance profiles of MTB, therefore it has extremely broad clinical application prospects.

Publisher:
本研究探讨靶向高通量测序（tNGS）技术对诊断结核患者的利福平和利福布汀耐药的应用价值。采用回顾性队列研究，收集2020—2023年深圳市第三人民医院119例培养阳性结核患者的分枝杆菌菌株，tNGS检测rpoB基因耐药突变情况，其中46株结核分枝杆菌（MTB）中检出了14种不同型别的rpoB基因突变，包括43例rpoB基因耐药相关突变和3例529位密码子同义突变。以利福平及利福布汀最小抑菌浓度（MIC）表型药敏结果为金标准，tNGS方法检测利福平和利福布汀耐药的敏感度均为100%，特异度为96.2%和89.4%，具有良好的诊断性能。其中rpoB基因531、526位突变与利福平和利福布汀的耐药高度相关。在此基础上，tNGS检测23例结核患者临床原始痰标本与对应菌株结果一致，对18例多次分枝杆菌培养阳性患者的83株MTB菌株进行tNGS检测，结果显示2例MTB初始无突变患者后续检出rpoB基因突变同时利福平和利福布汀表型药敏变为耐药。综上，tNGS检测可显示rpoB基因突变类型，减少同义突变造成的假阳性结果，对诊断利福平和利福布汀耐药具有良好的检验性能；tNGS可直接检测临床痰标本，还可用于动态监测MTB分子耐药谱变化。.

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PMID: 39537404 [Indexed for MEDLINE]

40. Insights to the role of phytoconstituents in aiding multi drug resistance - Tuberculosis treatment strategies.

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Multidrug resistant tuberculosis (MDR-TB) have emerged as a global challenge. There are several underlying mechanisms which are involved in causing mycobacterial resistance towards antitubercular agents including post translational modifications, efflux pumps and gene mutations. This resistance necessitates the investigation of complementary therapeutic options including the use of bioactive compounds from plants. Recent studies have focused on recognising and isolating the characteristics of these compounds to assess their potential against MDR-TB. Phytoconstituents such as alkaloids, flavonoids, terpenoids, glycosides, and essential oils have shown promising antimicrobial activity against Mycobacterium tuberculosis. These compounds can either directly kill or inhibit the growth of M. tuberculosis or enhance the immune system's ability to fight against the infection. Some studies suggest that combining phytoconstituents with standard antitubercular medications works synergistically by enhancing the efficacy of drug, potentially lowering the associated risk of side effects and eventually combating resistance development. This review attempts to elucidate the potential of phytoconstituents in combating resistance in MDR-TB which hold a promise to change the course of treatment strategies in tuberculosis.

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41. Population-level frequency of fluoroquinolone resistance by whole-genome sequencing drug predictions in Mycobacterium tuberculosis complex isolates in England from 2017-2023.

Clin Infect Dis. 2024 Nov 13:ciae560. doi: 10.1093/cid/ciae560. Online ahead of print.

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Fluoroquinolones are an important component of anti-tuberculosis treatment and identifying fluoroquinolone resistance is essential. We present the first survey of fluoroquinolone resistance in England from sequencing of over 16,000 unselected isolates. Fluoroquinolone resistance was 1.4% overall and 23.9% in multidrug-resistant TB. Routine sequencing allows resistance surveillance and should be widely adopted.

DOI: 10.1093/cid/ciae560
PMID: 39535753

42. Identification of novel DNA Gyrase inhibitor by combined Pharmacophore modeling, QSAR analysis, Molecular docking, Molecular dynamics, ADMET and DFT approaches.

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DNA gyrase, an ATP-dependent enzyme, plays a critical role in DNA replication, transcription, and recombination in Mycobacterium tuberculosis (MTB). While fluoroquinolones are effective antibacterial agents targeting DNA gyrase, their clinical use is often limited due to side effects and the emergence of bacterial resistance. In this study, we developed a quantitative structure-activity relationship (QSAR) model to predict the anti-tubercular activity of Quinoline-Aminopiperidine derivatives targeting the DNA gyrase enzyme, using a dataset of 48 compounds obtained from the literature. The QSAR model was validated using both internal and external validation metrics. Model 4, the best predictive model, demonstrated a strong fit with an R^2 of 0.8393, an adjusted R^2 (R^2adj) of 0.8010, and a lack of fit (LOF) parameter of 0.0626. The QSAR results revealed that DNA gyrase inhibition is significantly influenced by factors such as partition coefficient, molecular flexibility, hydrogen bonding potential, and the presence of fluorine atoms. Twelve quinoline-aminopiperidine derivatives were designed, and their anti-tubercular activity was predicted using QSAR model-4. These compounds were further assessed for pharmacokinetic properties, toxicity, and binding affinity to DNA gyrase. Pharmacophore modeling was also performed and validated using MOE software. The final pharmacophore model includes the features of two aromatic hydrophobic features, one hydrogen bond acceptor, and one hydrogen bond donor. The results indicated that designed compounds QA-3 and dataset compounds C-34 exhibit favorable drug-likeness properties. Molecular dynamics simulations confirmed the stable binding of compounds QA-3 and C-34 to the DNA gyrase protein, highlighting their potential as promising anti-tubercular agents. The developed QSAR Model-4 will facilitate the prediction of anti-tubercular activity in Quinoline-Aminopiperidine derivatives.

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paper.

43. Assay Development for High-Throughput Drug Screening Against Mycobacteria.

J Vis Exp. 2024 Oct 25;(212). doi: 10.3791/66860.

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Mycobacterium abscessus (Mab) infections are challenging to treat due to high intrinsic drug resistance, comparable to multidrug-resistant tuberculosis. Treatments are extremely ineffective and based on a multi-drug regimen, resulting in low patient compliance. Consequently, the scientific community is urged to identify new and effective drugs to treat these infections. One of the strategies employed to this end is drug repurposing - the process of identifying new therapeutic opportunities for existing drugs in the market, circumventing the time required to establish pharmacokinetic and safety profiles of new drugs. With most studies on drug development against Mab relying on traditional and time-consuming methods, an assay for high-throughput drug screening was developed against mycobacteria using an in house developed double-reporter strain of Mab. Using liquid-handling robotics, automated microscopy, and analysis, alongside in house developed double reporter strains, bacterial viability can be rapidly measured using two different readouts, luminescence and fluorescence, without adding reagents or performing any extra steps. This reduces time and variability between assays, a major advantage for high-throughput screenings. The described protocol was validated by screening a library of 1280 compounds. The obtained results were corroborated by the literature, with efficient detection of active compounds. Thus, this work

fulfilled the aim of supplying the field with a new tool to help fight this extremely drug-resistant bacteria.

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44. In vitro monitoring of drug resistance emergence during stepwise induction of bedaquiline and clofazimine, alone and in combination: a phenotypic and genotypic analysis.

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OBJECTIVES: The co-resistance between bedaquiline and clofazimine raises significant concerns, as they are commonly co-administered as core drugs in drug-resistant TB regimens. The present study aimed to monitor drug resistance-associated gene mutations and the phenotypic change in Mycobacterium tuberculosis (Mtb) under a stepwise drug resistance induction in vitro using bedaquiline, clofazimine or combined drugs.
METHODS: Drug-resistant Mtb strains were gradually induced in vitro on a drug-containing solid medium with a 2-fold increasing concentration of bedaquiline, clofazimine and their combination. The MIC of the induced drug-resistant Mtb strains was determined. The drug resistance-associated genes, including Rv0678, Rv1979c, atpE and pepQ, were sequenced and analysed.
RESULTS: Unlike exposure to bedaquiline alone or the combination of these two drugs, clofazimine alone resulted in drug resistance gene mutations occurring later, specifically in the fourth round of induction as opposed to the second round of induction. Besides, nucleotide deletion or insertion in Rv0678 was the main mutation type for induction under the two-drug combination, while single-nucleotide polymorphisms (SNPs) in Rv0678 were the major mutation types when induced by bedaquiline or clofazimine alone. Rv0678 mutation happened at a relatively lower bedaquiline concentration exposure alone, while atpE mutation

occurred at a higher bedaquiline concentration. Regardless of the drug exposure manner, a strong correlation between bedaquiline MICs and clofazimine MICs was observed in all drug resistance strains.
CONCLUSIONS: Combined exposure to bedaquiline and clofazimine developed Rv0678 mutation as early as exposure to bedaquiline alone. However, rather than SNPs, deletion and insertion were the dominant mutation types in dual-drug exposure strain.

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PMID: 39523472

45. Advancements and challenges in tuberculosis drug discovery: A comprehensive overview.

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Tuberculosis continues to pose a health challenge causing the loss of millions of lives despite the existence of multiple drugs, for treatment. The emergence of drug-resistant strains has made the situation more complex making it increasingly difficult to fight against this disease. This review outlines the challenges associated with TB drug discovery, the nature of Mycobacterium tuberculosis shedding light on the mechanisms that lead to treatment failure and antibiotic resistance. We explore promising drug targets, encompassing inhibition of mycolyarabinogalactan peptidoglycan (MAGP) assembly, mycolic acid biosynthesis, DNA replication, transcription, translation, protein synthesis, and bioenergetics/metabolism pathways. A comprehensive overview of the global pipeline of anti-tuberculosis drugs at various stages of clinical trials, the

diverse strategies being pursued to tackle this complex disease. By gaining an understanding of the mechanisms that contribute to resistance development and identifying suitable targets, we can pave the way for more effective treatments and contribute to global efforts to combat drug-resistant tuberculosis.

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46. Actor Sensemaking and its Role in Implementation of the Decentralized Drug-Resistant TB Policy in South Africa.

Health Policy Plan. 2024 Nov 7:czae105. doi: 10.1093/heapol/czae105. Online ahead of print.

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South Africa has a high burden of drug-resistant tuberculosis (DR-TB). A policy to decentralize DR-TB treatment from specialized central hospitals to more accessible district facilities was introduced in 2011, but to date implementation has been suboptimal, with variable pace, coverage and models of care emerging. This study explored multilevel policy implementation of DR-TB decentralization in two provinces of South Africa, Western Cape and KwaZulu-Natal. Applying interpretive policy analysis, this paper describes how actors across health system levels and geographies made sense of the DR-TB policy and how this shaped implementation. In an embedded qualitative case study, districts of the two provinces were compared, through data collected in 94 in-depth interviews, and analysed using Vickers' framework of reality, value and action judgements. Five district cases characterise variation in the pace of implementation and models of DR-TB care that emerged. Individual and collective

attitudes for and against the policy were underpinned by different systems of meaning for interpreting policy problems and making decisions. These meaning systems were reflected in actor stances on whether DR-TB care needed to be specialized or generalized, nurse- or doctor-led, and institutionalized or ambulatory. Actors' stances influenced their actions and implementation strategies adopted. Resistance to decentralized DR-TB care related to perceived threats of budget cuts to and loss of authority of central facilities, and was often justified in fears of increased transmission, poor quality of care and inadequate resources at lower levels. New advances in diagnosis and treatment to address the growing burden of DR-TB in South Africa will have little impact unless implementation dynamics are better understood, and attention paid to the mindsets, interests and interpretations of policy by actors tasked with implementation. Deliberative policy implementation processes will enhance the quality of discourse, communication and cross-learning between policy actors, critical for reaching synthesis of meaning systems.

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PMID: 39506555

47. Quinoline hybrid derivatives as effective structural motifs in the treatment of tuberculosis: Emphasis on structure-activity relationships.

Tuberculosis (Edinb). 2024 Nov 3;149:102573. doi: 10.1016/j.tube.2024.102573. Online ahead of print.

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Mycobacterium tuberculosis (MTB/Mtb) is the causative agent of tuberculosis

(TB), a highly infectious serious airborne illness. TB usually affects the lungs, in 25 % of patients (children or immune impaired adults), mycobacteria can enter the blood stream and infect other bodily areas such the meninges, pleura, lymphatic system, genitourinary system, bones, and joints. Currently, the most challenging aspect of treating this illness is the ineffectiveness of the most potent first-line anti-TB medications, isoniazid, rifampin, pyrazinamide, and ethambutol, which can result in multidrug-resistant TB (MDR-TB), extensively drug-resistant TB (XDR-TB), and in rare instances, completely drug-resistant TB (TDR-TB). As a result, finding new pharmaceutical compounds to treat these diseases is a significant challenge for the scientific community. A number of bio-active molecules have been investigated in this quest, including quinoline, which is considered a promising candidate for the development of TB drugs. It is known that quinoline are low in toxicity and have a wide range of pharmacological properties. Researchers have investigated quinoline scaffolds as anti-TB drugs based on their biological spectrum. The objective of this review is to examine the recent development of quinoline and its structural characteristics crucial to its antitubercular (anti-TB) activity. A molecular analog of the TB treatment can be designed and identified with this information. As a result, future generation quinoline-based anti-TB agents with greater potency and safety can also be explored.

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48. Analysis of genetic characteristics associated with reduced bedaquiline susceptibility in multidrug-resistant Mycobacterium tuberculosis.

Tuberculosis (Edinb). 2024 Oct 23;149:102572. doi: 10.1016/j.tube.2024.102572. Online ahead of print.

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Bedaquiline (BDQ) has shown efficacy in shortening treatment duration and enhancing treatment success rates for multidrug-resistant tuberculosis (MDR-TB), thereby prompting widespread adoption. However, resistance to BDQ has emerged. This study aimed to identify genetic characteristics associated with decreased susceptibility to BDQ, using a public database to aid in the detection of resistant strains. Seventy-one BDQ-resistant and 929 BDQ-susceptible isolates from the open-source CRyPTIC database were selected for analysis. Variant calling was conducted via the clockwork pipeline. Univariate logistic regression was performed for each gene mutation, followed by LASSO regression for further

variant selection. Ultimately, a multiple linear regression model was developed using log2-transformed Minimum Inhibitory Concentration values as the dependent variable, with variant selection refined through stepwise regression based on the Akaike Information Criterion. Ten gene mutations were significantly associated with reduced BDQ susceptibility, including two key gene mutations: Rv0678_141_ins_1 and Rv1979c_D249E, with effect estimates of 1.76 (95 % CI: 0.67-2.84) and 1.69 (95 % CI: 0.22-3.17), respectively. Other implicated genes included Rv2699c_-84_del_1, hsaB_I179T, mmpL9_T241A, pncA_C14R, Rv0373c_G621S, Rv0893c_L27F, Rv1770_A4D, and Rv3428c_S327C. This study identified ten gene mutations linked to decreased susceptibility to BDQ, providing a reference for developing a comprehensive catalog of BDQ-resistant genes.

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49. Method development and validation of an analytical quality by design ultrafast liquid chromatographic method for the determination of bedaquiline from pharmaceutical bulk and nanoemulsions.

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Bedaquiline (BDQ) is a drug used to treat multidrug-resistant tuberculosis (MDR-TB). It exhibits exposure-dependent efficacy in eliminating Mycobacterium tuberculosis (Mtb). An easy, efficient and precise reverse-phase ultrafast liquid chromatography (RP-UFLC) method was developed to validate the free base of the antitubercular medication BDQ. BDQ was separated using a 10:90 v/v mobile phase of ammonium acetate buffer solution (pH = 5.4) and high-performance liquid chromatography-grade methanol, with a flow rate of 1.5 mL/min and a UV detection wavelength of 226 nm. By using the Box-Behnken design (BBD) and response surface methodology (RSM), the method was optimised by varying critical analytical attributes (CAA) and critical performance attributes (CPAs) namely ammonium acetate fraction (%), flow rate (ml/min), buffer system molarity (M) and pH. BDQ

was eluted at 7.5 min utilising isocratic elution. The method was linear in the concentration range of 0.5-300 µg/mL with limit of detection values of 0.039 µg/mL and limit of quantification of 0.12 µg/mL. The results indicate that this validated method can be used as an alternative method for assay of BDQ.

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50. Incidence, types and predictors of adverse events and their impact on treatment outcomes in multidrug/rifampicin resistant tuberculosis patients receiving all oral treatment regimens.

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BACKGROUND: Patients suffering from multidrug/rifampicin resistant tuberculosis (MDR/RR-TB) are treated for prolonged periods with a complex regimen comprised of relatively less effective and more toxic anti-TB drugs, consequently resulting in high incidence of adverse events (AEs).
STUDY AIM: The current study evaluates the incidence, types, management and predictors of AEs, and their impact on treatment outcomes in MDR/RR-TB patients receiving all oral treatment regimens.
STUDY DESIGN: A total of 242 eligible MDR/RR-TB patients treated at two different study sites from June 2019 to December 2021 were included in this study.
MEASURES AND OUTCOMES: Patients' sociodemographic, microbiological, clinical characteristics, reported AEs and treatment outcomes were retrospectively

abstracted from their medical records. Chi-square, and Fisher exact tests (wherever applicable) were used to find the association between the variable and the occurrence of AEs.
RESULTS: Majority of the patients were suffered from MDR-TB (71.9%) and were treated with longer treatment regimen (77.7%). Overall 206/242 patients (85%) experienced at least one AE during their treatment. Gastrointestinal disturbance was the most common AE (49.6%), followed by arthralgia (49.2%), psychiatric disturbances (39.3%), dermatological reactions (27.7%), body/headache (24.8%) and hyperuricemia (19%). Due to AEs, treatment modification was noted in 55 (22.72%) patients. Level of modification in the treatment regimen was higher in optic neuritis (100%) followed by neuropathies (80%) and myelosuppression (59%). Similarly, hepatotoxicity was the most serious AE in which the whole treatment regimen was terminated in 27% of patients. Furthermore, the results revealed that only patients' education status had statistically significant association with the incidence of AEs ($p = 0.02$). The treatment success rate was 80.6% whereas the ratio of died and LTFU patients were 15.3% and 4.1% respectively. Although patients who experienced AEs were more likely to develop successful treatment outcomes (82%) than their counterparts (72.2%), though this difference was not statistically significant.
CONCLUSION: Although AEs were highly present in the current cohort, but they were successfully managed mostly by nonpharmacological interventions or symptomatic treatment. Besides, the incidence of AEs did not have a negative impact on treatment outcomes. High-risk patients for AEs must receive special attention and enhanced clinical management.

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PMID: 39494731

51. Evaluating culture-free targeted next-generation sequencing for diagnosing drug-resistant tuberculosis: a multicentre clinical study of two end-to-end commercial workflows.

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BACKGROUND: Drug-resistant tuberculosis remains a major obstacle in ending the global tuberculosis epidemic. Deployment of molecular tools for comprehensive drug resistance profiling is imperative for successful detection and characterisation of tuberculosis drug resistance. We aimed to assess the diagnostic accuracy of a new class of molecular diagnostics for drug-resistant tuberculosis.
METHODS: We conducted a prospective, cross-sectional, multicentre clinical evaluation of the performance of two targeted next-generation sequencing (tNGS) assays for drug-resistant tuberculosis at reference laboratories in three countries (Georgia, India, and South Africa) to assess diagnostic accuracy and index test failure rates. Eligible participants were aged 18 years or older, with molecularly confirmed pulmonary tuberculosis, and at risk for rifampicin-resistant tuberculosis. Sensitivity and specificity for both tNGS index tests (GenoScreen Deeplex Myc-TB and Oxford Nanopore Technologies [ONT] Tuberculosis Drug Resistance Test) were calculated for rifampicin, isoniazid, fluoroquinolones (moxifloxacin, levofloxacin), second line-injectables (amikacin, kanamycin, capreomycin), pyrazinamide, bedaquiline, linezolid, clofazimine, ethambutol, and streptomycin against a composite reference standard of phenotypic drug susceptibility testing and whole-genome sequencing.
FINDINGS: Between April 1, 2021, and June 30, 2022, 832 individuals were invited to participate in the study, of whom 720 were included in the final analysis (212, 376, and 132 participants in Georgia, India, and South Africa, respectively). Of 720 clinical sediment samples evaluated, 658 (91%) and 684 (95%) produced complete or partial results on the GenoScreen and ONT tNGS workflows, respectively, with 593 (96%) and 603 (98%) of 616 smear-positive samples producing tNGS sequence data. Both workflows had sensitivities and specificities of more than 95% for rifampicin and isoniazid, and high accuracy for fluoroquinolones (sensitivity approximately ≥94%) and second line-injectables (sensitivity 80%) compared with the composite reference standard. Importantly, these assays also detected mutations associated with resistance to critical new and repurposed drugs (bedaquiline, linezolid) not currently detectable by any other WHO-recommended rapid diagnostics on the market. We note that the current format of assays have low sensitivity (≤50%) for linezolid and more work on mutations associated with drug resistance is

needed.
INTERPRETATION: This multicentre evaluation demonstrates that culture-free tNGS can provide accurate sequencing results for detection and characterisation of drug resistance from Mycobacterium tuberculosis clinical sediment samples for timely, comprehensive profiling of drug-resistant tuberculosis.
FUNDING: Unitaid.

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PMID: 39486428

Conflict of interest statement: Declaration of interests TCR, MS, and REC received salary support from FIND through a service contract to UC San Diego. TCR and REC received grant funding from the US National Institutes of Health to develop and evaluate a tNGS solution for drug-resistant tuberculosis (R01AI176401). TCR and REC are co-inventors on a patent associated with the processing of tuberculosis sequencing data (European Patent Application number 14840432.0 and USSN 14/912,918). Both TCR and REC have transferred all rights and present and future interest in and rights to royalties from this patent to UC San Diego and the Translational Genomics Research Institute, respectively. TCR is a co-founder, board member, and unpaid shareholder of Verus Diagnostics, a company that was founded with the intent of developing diagnostic assays. Verus Diagnostics is not pursuing any drug-resistant tuberculosis diagnostics nor any diagnostics related to the technology or approaches discussed or mentioned in this manuscript. Verus Diagnostics was not involved in any way with data collection, analysis, or publication of the results of this manuscript. TCR has not received any financial support from Verus Diagnostics. CR has received honoraria payments from Becton Dickinson and she is on the scientific advisory board for Cepheid and bioMérieux. All other authors declare no competing interests.

52. Drug repurposing: An antidiabetic drug Ipragliflozin as Mycobacterium tuberculosis sirtuin-like protein inhibitor that synergizes with anti-tuberculosis drug isoniazid.

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The surge of drug-resistant Mycobacterium tuberculosis (DR-TB) impedes the World Health Organization's efforts in ending TB and calls for new therapeutic formulations. M. tuberculosis sirtuin-like protein Rv1151c is a bifunctional enzyme with both deacetylation and desuccinylation activities, which plays an important role in M. tuberculosis drug resistance and stress responses. Thus, it appears to be a promising target for the development of new TB therapeutics. In this study, we screened 31,057 ligand compounds from seven compound libraries in silico to identify inhibitors of Rv1151c. Ipragliflozin can bind to Rv1151c and interact stably. Ipragliflozin can change the acylation level of M. tuberculosis by inhibiting Rv1151c and effectively inhibit the growth of M. tuberculosis H37Rv and M. smegmatis. It can potentiate the first-front anti-TB drug isoniazid. As an antidiabetic drug, Ipragliflozin can be potentially included in the regimen to treat diabetes-tuberculosis comorbidity.

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PMID: 39481722

Conflict of interest statement: Declaration of competing interest The authors have no relevant financial or non-financial interests to disclose.

53. Risk factors for and timing of presumptive recurrent TB.

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<sec><title>INTRODUCTION</title>Understanding factors associated with increased risk for tuberculosis (TB) recurrence is essential in lowering the TB burden. We aimed to quantify the burden, risk factors, and timing of TB presumptive recurrence.</sec><sec><title>METHODS</title>We analyzed test results from 2013 to 2017 in the South African National Health Laboratory Service's database. We defined a person's TB episode to start with their first positive TB test. In the absence of treatment outcome data, we assumed the episode concluded 6 months later for rifampicin-susceptible TB (RS-TB) and 18 months later for rifampicin-resistant TB (RR-TB), provided that at least one negative smear or culture test was recorded within this period. We defined a presumptive recurrent TB episode to start with a positive TB test after the completion of a prior episode. We calculated recurrence measures stratified by various demographics and RR-TB status.</sec><sec><title>RESULTS</title>Of 574,316 people with RS-TB, 4.7% experienced at least one presumptive recurrent TB episode. Higher local TB notification rates, HIV coinfection, and males experienced higher recurrence rates. Most (89.4%) of the first RS-TB recurrences occurred within a year of the

initial episode.</sec><sec><title>CONCLUSION</title>Our findings of when and among whom recurrent TB is more likely to occur can be used to assist early interventions and inform impact on patient care.</sec>.

DOI: 10.5588/ijtld.24.0019
PMID: 39468024 [Indexed for MEDLINE]

54. Molecular Indicator for Distinguishing Multi-drug-Resistant Tuberculosis from Drug Sensitivity Tuberculosis and Potential Medications for Treatment.

Mol Biotechnol. 2024 Oct 24. doi: 10.1007/s12033-024-01299-z. Online ahead of print.

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The issue of multi-drug-resistant tuberculosis (MDR-TB) presents a substantial challenge to global public health. Regrettably, the diagnosis of drug-resistant tuberculosis (DR-TB) frequently necessitates an extended period or more extensive laboratory resources. The swift identification of MDR-TB poses a particularly challenging endeavor. To identify the biomarkers indicative of multi-drug resistance, we conducted a screening of the GSE147689 dataset for differentially expressed genes (DEGs) and subsequently conducted a gene enrichment analysis. Our analysis identified a total of 117 DEGs, concentrated in pathways related to the immune response. Three machine learning methods, namely random forest, decision tree, and support vector machine recursive feature elimination (SVM-RFE), were implemented to identify the top 10 genes according to their feature importance scores. A4GALT and S1PR1, which were identified as common genes among the three methods, were selected as potential molecular markers for distinguishing between MDR-TB and drug-susceptible tuberculosis (DS-TB). These markers were subsequently validated using the GSE147690 dataset. The findings suggested that A4GALT exhibited area under the curve (AUC) values of 0.8571 and 0.7121 in the training and test datasets, respectively, for distinguishing between MDR-TB and DS-TB. S1PR1 demonstrated

AUC values of 0.8163 and 0.5404 in the training and test datasets, respectively. When A4GALT and S1PR1 were combined, the AUC values in the training and test datasets were 0.881 and 0.7551, respectively. The relationship between hub genes and 28 immune cells infiltrating MDR-TB was investigated using single sample gene enrichment analysis (ssGSEA). The findings indicated that MDR-TB samples exhibited a higher proportion of type 1 T helper cells and a lower proportion of activated dendritic cells in contrast to DS-TB samples. A negative correlation was observed between A4GALT and type 1 T helper cells, whereas a positive correlation was found with activated dendritic cells. S1PR1 exhibited a positive correlation with type 1 T helper cells and a negative correlation with activated dendritic cells. Furthermore, our study utilized connectivity map analysis to identify nine potential medications, including verapamil, for treating MDR-TB. In conclusion, our research identified two molecular indicators for the differentiation between MDR-TB and DS-TB and identified a total of nine potential medications for MDR-TB.

DOI: 10.1007/s12033-024-01299-z
PMID: 39446300

55. Prevalence of rifampicin and isoniazid mono-resistance among cases of pulmonary tuberculosis from Western Uttar Pradesh, North India.

Mol Biol Rep. 2024 Oct 24;51(1):1091. doi: 10.1007/s11033-024-10014-9.

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BACKGROUND: Mono-resistance to rifampicin/isoniazid increases poor treatment outcomes and the risk of multi-drug resistance (MDR) in tuberculosis (TB) patients. Limited information exists about mono-resistance status of TB patients in Uttar Pradesh, North India. This study aimed to estimate the burden of rifampicin and isoniazid mono-resistance in Western Uttar Pradesh.

METHODS AND RESULTS: 153 sputum samples of suspected pulmonary tuberculosis patients were processed to isolate Mycobacterium tuberculosis using the Lowenstein-Jensen (L-J) culture medium. The isolates were identified using an immuno-chromatographic test and IS6110 PCR. The confirmed Mycobacterium tuberculosis isolates were tested for drug susceptibility testing against rifampicin and isoniazid anti-tuberculosis drugs. The results of the drug susceptibility testing were compared with demographic information and analyzed statistically. Out of 153 sputum samples, 83 (54.24%) samples were positive for growth on L-J medium, including 82 (98.79%) Mycobacterium tuberculosis isolates. Of the 82 Mycobacterium tuberculosis isolates, 16 (19.51%), 7 (8.54%), and 5 (6.10%) isolates were MDR, mono-resistant to rifampicin and isoniazid, respectively. The occurrence of RIF/INH mono-resistant-TB was higher in patients of male gender, age above 45 years, living in rural conditions, history of weight loss, and previous anti-TB treatment, but the effect was not statistically significant.
CONCLUSIONS: The study reported the status of rifampicin and isoniazid mono-resistance among TB patients and highlighted the need for continuous monitoring and improved intervention for the initial detection of mono-drug-resistant cases. This will improve clinical treatment outcomes and decrease the rate of drug-resistant TB in Uttar Pradesh, North India.

DOI: 10.1007/s11033-024-10014-9
PMID: 39446249 [Indexed for MEDLINE]

56. Pulmonary tuberculosis in non-HIV adults: an evergreen old-fashioned disease in high-income countries. A narrative review.

Expert Rev Respir Med. 2024 Nov;18(11):861-872. doi: 10.1080/17476348.2024.2418932. Epub 2024 Oct 28.

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INTRODUCTION: Tuberculosis (TB), an infective air-borne disease with worldwide non-homogeneous distribution, remains a top cause of morbidity and mortality. TB

control is linked to early diagnosis and proper treatment of contagious TB cases and infected subjects at high risk of developing TB.
AREAS COVERED: A narrative review of pulmonary TB in non-HIV adults with reference to high-income countries. Modern medicine offers several advancements in diagnostics and therapeutics of TB, but they often remain to be extensively implemented in real life. In high-income countries TB is now relatively uncommon, but it remains a health and socio-economic burden that should not be underestimated.
EXPERT OPINION: Pulmonologists should maintain expertise toward TB for several reasons. First, the lung is the most common and the infectious moiety of TB. Second, TB remains a global issue due to common travels of western people and migrations from areas with high incidence of TB. Third, as TB has heterogenous clinics, its prompt diagnosis may be difficult. Fourth, TB is a curable disease, but its management is complex and predisposes to poor adherence with failures/relapses and selection of drug-resistant strains.

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PMID: 39434706 [Indexed for MEDLINE]

57. Exploring gene mutations and multidrug resistance in Mycobacterium tuberculosis: a study from the Lung Hospital in Vietnam.

Mol Biol Rep. 2024 Oct 21;51(1):1084. doi: 10.1007/s11033-024-10015-8.

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BACKGROUND: Drug-resistant tuberculosis not only diminishes treatment efficacy but also heightens the risk of transmission and mortality. Investigating Mycobacterium tuberculosis resistance to first-line antituberculosis drugs is essential to tackle a major global health challenge.
METHODS AND RESULTS: Using Sanger sequencing, this study investigates gene mutations associated with multidrug resistance in drug-resistant M. tuberculosis strains. Among 30 samples, mutations were found in genes linked to first-line anti-tuberculosis drug resistance. Rifampicin resistance was observed in 46.67% of the samples, with the most frequent mutation in the rpoB gene at codon 450 (S450L) occurring in 23.33% of cases. Similarly, isoniazid resistance was found

in 86.67% of samples, with 33.33% of cases indicating the katG gene mutation at codon 315 (S315T). Additionally, streptomycin resistance was present in 76.67% of samples, and 30% of these cases were mainly linked to the rpsL gene mutation at codon 43 (K43R).
CONCLUSION: These findings illuminate the genetic mechanisms behind drug resistance in M. tuberculosis. By identifying specific genetic markers, this research enhances our ability to diagnose and treat drug-resistant Tuberculosis more accurately and efficiently.

DOI: 10.1007/s11033-024-10015-8
PMID: 39432118 [Indexed for MEDLINE]

58. Mycobacterium tuberculosis inhibitors: an updated patent review (2021-present).

Expert Opin Ther Pat. 2024 Nov 18:1-16. doi: 10.1080/13543776.2024.2419826. Online ahead of print.

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INTRODUCTION: Tuberculosis (TB) remains a major global health issue, causing around 10 million new cases and 1.3 million deaths in 2022. The challenge is compounded by multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB strains, and co-infection with HIV.
AREAS COVERED: The present review examines significant patent literature on TB chemotherapeutics from September 2021 to the present using the following databases, reaxys, google patent and espacenet. Only patents reporting compounds with a minimum inhibitory concentration (MIC) on whole Mycobacterium tuberculosis cells of ≤5 μM were selected for review.
EXPERT OPINION: The fight against TB is advancing with the development of promising new compounds due to the challenge of drug-resistant strains. Notable among those reviewed in this paper are the benzothiazinones, showing high efficacy against both drug-sensitive and resistant TB strains. Additionally, Q203 analogues, demonstrate strong antitubercular activity, good microsomal stability, and favorable safety profiles. Finally, LysRS inhibitors also show significant promise in vivo models. These advancements underscore the importance of novel targets and innovative strategies in developing effective, resistance-resistant TB treatments.

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PMID: 39431728

59. Levofloxacin activity at increasing doses in a murine model of fluoroquinolone-susceptible and -resistant tuberculosis.

Antimicrob Agents Chemother. 2024 Nov 6;68(11):e0058324. doi: 10.1128/aac.00583-24. Epub 2024 Oct 16.

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High-dose levofloxacin was explored in a clinical trial against multidrug-resistant tuberculosis and failed to show increased efficacy. In this study, we used a murine model to explore the efficacy of a dose increase in levofloxacin monotherapy beyond the maximum dose evaluated in humans. A total of 120 4-week-old female BALB/c mice were intravenously infected with 106 CFU of Mycobacterium tuberculosis H37Rv wild-type (WT) or isogenic H37Rv mutants harboring GyrA A90V or D94G substitutions; the MICs were 0.25, 4, and 6 µg/mL, respectively. Levofloxacin 250 and 500 mg/kg were given every 12 h (q12h) orally for 4 weeks. Pharmacokinetic parameters were determined after five doses. These two regimens decreased lung bacillary load in mice infected with H37Rv WT but not in mice infected with the A90V and D94G mutants. Levofloxacin 250 mg/kg q12h in mice generated pharmacokinetic parameters equivalent to 1,000 mg/d in humans, whereas 500 mg/kg q12h generated a twofold greater exposure than the highest equivalent dose tested in humans (1,500 mg/d). In our dose-response model, the effective concentration at 50% (EC50) produced an AUC/MIC (AUC0-24h/MIC) ratio of 167.9 ± 27.5, and at EC80 it was 281.2 ± 97.3. Based on this model, high-dose levofloxacin regimens above 1,000 mg/d are not expected to cause a significant increase in bactericidal activity. This study suggests no benefit of high-dose levofloxacin above 1,000 mg/d in the treatment of fluoroquinolone-susceptible or -resistant tuberculosis.

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PMCID: PMC11539234
PMID: 39412267 [Indexed for MEDLINE]

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

60. Challenges and potential solutions for cycloserine dosing in patients with sepsis undergoing continuous renal replacement therapy.

Int J Antimicrob Agents. 2024 Nov;64(5):107345. doi: 10.1016/j.ijantimicag.2024.107345. Epub 2024 Sep 23.

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Continuous kidney replacement therapy (CRRT) is a special form of dialysis, which has more significant advantages than traditional intermittent hemodialysis in treating critically ill patients. The impact of CRRT and disease complexity on drug clearance in critically ill patients has been reported in several studies; nevertheless, the pharmacokinetic changes of cycloserine in patients with sepsis undergoing CRRT have not been reported. Here, we report a case of a 52-year-old man with septic shock and severe multidrug-resistant tuberculosis who underwent anti-tuberculosis (anti-TB) therapy. The patient's anti-TB regimen included linezolid, clofazimine, cycloserine, and bedaquiline. Following continuous administration for 14 days, the patient was treated with CRRT due to acid-base imbalance and acute renal failure. Blood samples were collected at 0, 2, 4, 6, 10, and 12 hours following cycloserine administration (CRRT was initiated 2 hours after administration). Changes in plasma concentration of cycloserine before and after CRRT were measured. The peak concentration of cycloserine was 39.93 mg/L with a trough concentration of 7.90 mg/L, and the AUC0-12h was 294.36 mg·h/L. These findings suggest that the pharmacokinetics of cycloserine may be influenced by sepsis and CRRT therapy, and that cycloserine doses may need to be increased during CRRT therapy in patients with sepsis.

DOI: 10.1016/j.ijantimicag.2024.107345
PMID: 39321892 [Indexed for MEDLINE]

61. Pharmacokinetics of anti-TB drugs in children and adolescents with drug-resistant TB: a multicentre observational study from India.

J Antimicrob Chemother. 2024 Nov 4;79(11):2939-2947. doi: 10.1093/jac/dkae311.

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Erratum in
J Antimicrob Chemother. 2024 Nov 12:dkae421. doi: 10.1093/jac/dkae421.

BACKGROUND: Drug-resistant tuberculosis (DR-TB) is one of the challenging forms

of TB to treat, not only in adults but also in children and adolescents. Further, there is a void in the treatment strategy exclusively for children due to various reasons, including paucity of pharmacokinetic (PK) data on anti-TB drugs across the globe. In this context, the present study aimed at assessing the PK of some of the anti-TB drugs used in DR-TB treatment regimens.
METHOD: A multicentre observational study was conducted among DR-TB children and adolescents (n = 200) aged 1-18 years (median: 12 years; IQR: 9-14) treated under programmatic settings in India. Steady-state PK (intensive: n = 89; and sparse: n = 111) evaluation of moxifloxacin, levofloxacin, cycloserine, ethionamide, rifampicin, isoniazid and pyrazinamide was carried out by measuring plasma levels using HPLC methods.
RESULTS: In the study population, the frequency of achieving peak plasma concentrations ranged between 13% (for rifampicin) to 82% (for pyrazinamide), whereas the frequency of suboptimal peak concentration for pyrazinamide, cycloserine, moxifloxacin, levofloxacin and rifampicin was 15%, 19%, 29%, 41% and 74%, respectively. Further, the frequency of supratherapeutic levels among patients varied between 3% for pyrazinamide and 60% for isoniazid. In the below-12 years age category, the median plasma maximum concentration and 12 h exposure of moxifloxacin were significantly lower than that of the above-12 years category despite similar weight-adjusted dosing.
CONCLUSIONS: Age significantly impacted the plasma concentration and exposure of moxifloxacin. The observed frequencies of suboptimal and supratherapeutic concentrations underscore the necessity for dose optimization and therapeutic drug monitoring in children and adolescents undergoing DR-TB treatment.

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62. A sensitive, rapid and cost-effective RP-HPLC-UV method for detection and quantification of bedaquiline in physiological fluid (pH 7.4).

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Bedaquiline, a highly lipophilic molecule, is used in the treatment regimen of multi-drug resistant tuberculosis. A rare complication of pulmonary tuberculosis is tuberculous pericarditis. Ex vivo studies utilising animal pericardium can be used to investigate whether this drug is capable of diffusing across pericardial tissue into simulated pericardial fluid (pH 7.4) to indicate efficacy. For detection of bedaquiline in physiological fluid, a rapid, cost-effective and sensitive method is essential. The aim of this study was thus to develop and validate a simple and sensitive RP-HPLC-UV method for the detection and quantification of bedaquiline, encapsulated in a nanosystem, at pH 7.4 after permeation across excised pericardium. A HPLC Phenomenex Kinetex RPC18 column (150 × 4.6 mm, 5 µm) was utilized for analysis. The mobile phase consisted of 95 : 5 v/v (A : B), where (A) methanol : acetonitrile (85 : 15 v/v) : (B) triethylamine (1% v/v) : 0.15 mM KH_2PO_4 buffer (pH 7.4). Running conditions included the following: injection volume 20 µl, flow rate 1.0 ml min-1, detection wavelength 275 nm, 25 °C and running time of 5 min. Bedaquiline eluted as a single symmetrical peak at a retention time of 4.17 min. The method was found to be linear within the range of 1-50 µg ml-1 ($R^2 = 1$). The limit of detection (LOD) and limit of quantification (LOQ) were found to be 0.05 µg ml-1 and 0.15 µg ml-1, respectively (signal-to-noise ratio method). All validation parameters were found to be within acceptable limits (RSD < 2%). The method was fast, reliable, accurate, reproducible, and transient for the detection of bedaquiline in simulated physiological fluid (pH 7.4). This method can thus be applied to easily detect bedaquiline in body fluids (pH 7.4) i.e. blood and pericardial fluid without the accuracy being impacted by ionisation factors of the molecule.

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63. Exploring the Chemical Space of Mycobacterial Oxidative Phosphorylation Inhibitors Using Molecular Modeling.

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Mycobacteria are opportunistic intracellular pathogens that have plagued humans and other animals throughout history and still are today. They manipulate and hijack phagocytic cells of immune systems, enabling them to occupy this peculiar infection niche. Mycobacteria exploit a plethora of mechanisms to resist antimicrobials (e. g., waxy cell walls, efflux pumps, target modification, biofilms, etc.) thereby evolving into superbugs, such as extensively drug-resistant tuberculosis (XDR TB) bacilli and the emerging pathogenic Mycobacterium abscessus complex. This review summarizes the mechanisms of action of some of the surging antimycobacterial strategies. Exploiting the fact that mycobacteria are obligate aerobes and the differences between their oxidative phosphorylation pathways versus their human counterpart opens a promising avenue for drug discovery. The polymorphism of respiratory complexes across mycobacterial pathogens imposes challenges on the repositioning of antimycobacterial agents to battle the rise in nontuberculous mycobacterial infections. In silico strategies exploiting mycobacterial respiratory machinery data to design novel therapeutic agents are touched upon. The potential druggability of mycobacterial respiratory elements is reviewed. Future research addressing the health challenges associated with mycobacterial pathogens is discussed.

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64. Therapeutic drug monitoring in tuberculosis.

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PURPOSE: Therapeutic drug monitoring (TDM) is a standard clinical procedure that uses the pharmacokinetic and pharmacodynamic parameters of the drug in the body to determine the optimal dose. The pharmacokinetic variability of the drug(s) is a significant contributor to poor treatment outcomes, including the development of acquired drug resistance. TDM aids in dose optimization and improves outcomes while lessening drug toxicity. TDM is used to manage patients with tuberculosis (TB) who exhibit a slow response to therapy, despite good compliance and drug-susceptible organisms. Additional indications include patients at risk of malabsorption or delayed absorption of TB drugs and patients with drug-drug interaction and drug toxicity, which confirm compliance with therapy. TDM usually requires two blood samples: the 2 h and the 6 h post-dose. This narrative review will discuss the pharmacokinetics and pharmacodynamics of TB drugs, determinants of poor response to therapy, indications of TDM, methods of performing TDM, and its interpretations.
METHODS: This is a narrative review. We searched PubMed, Embase, and the CINAHL from inception to April 2024. We used the following search terms: tuberculosis, therapeutic drug monitoring, anti-TB drugs, pharmacokinetics, pharmacodynamics, limited sample strategies, diabetes and TB, HIV and TB, and multidrug-resistant TB. All types of articles were selected.
RESULTS: TDM is beneficial in managing TB, especially in patients with slow responses, drug-resistance TB, recurrent TB, and comorbidities such as diabetes mellitus and human immunodeficiency virus infection.
CONCLUSION: TDM is beneficial for improving outcomes, reducing the risk of acquired drug resistance, and avoiding side effects.

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65. Recent advances and challenges of revolutionizing drug-resistant tuberculosis treatment.

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Tuberculosis (TB), an infectious disease induced by Mycobacterium tuberculosis, is one of the primary public health threats all over the world. Since the prevalence of first-line anti-TB agents, the morbidity and mortality issues of TB descended obviously. Nevertheless, the emergences of multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains, the double prevalence of HIV-TB co-infection, and the insufficiency of plentiful health care have led to an increased incidence of TB. It is noted that current drugs for treating TB have proved unsustainable in the face of highly resistant strains. Fortunately, five categories of new drugs and candidates with new mechanisms of action have emerged in the field of anti-TB research after decades of stagnation in the progression of anti-TB drugs. In this paper, the research status of these promising anti-TB drugs and candidates are reviewed, emphasizing the challenges to be addressed for efficient development of future TB therapies.

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66. Development of a proliposomal pretomanid dry powder inhaler as a novel alternative approach for combating pulmonary tuberculosis.

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Multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) continue as public health concerns. Inhaled drug therapy for TB has substantial benefits in combating the causal agent of TB (Mycobacterium tuberculosis). Pretomanid is a promising candidate in an optional combined regimen for XDR-TB. Pretomanid has demonstrated high potency against M. tuberculosis in both the active and latent phases. Conventional spray drying was used to formulate pretomanid as dry powder inhalers (DPIs) for deep lung delivery using a proliposomal system with a trehalose coarse excipient to enhance the drug solubility. Co-spray drying with L-leucine protected hygroscopic trehalose in formulations and improved powder aerosolization. Higher amounts of L-leucine (40-50 % w/w) resulted in the formation of mesoporous particles with high percentages of drug content and entrapment efficiency. The aerosolized powders demonstrated both geometric and median aerodynamic diameters < 5 μm with > 90 % emitted dose and > 50 % fine particle fraction. Upon reconstitution in simulated physiological fluid, the proliposomes completely converted to liposomes, exhibiting suitable particle sizes (130-300 nm) with stable colloids and improving drug solubility, leading to higher drug dissolution compared to the drug alone. Inhalable pretomanid showed

higher antimycobacterial activity than pretomanid alone. The formulations were safe for all broncho-epithelial cell lines and alveolar macrophages, thus indicating their potential suitability for DPIs targeting pulmonary TB.

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67. Machine learning investigation of tuberculosis with medicine immunity impact.

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Tuberculosis (T.B.) remains a prominent global cause of health challenges and death, exacerbated by drug-resistant strains such as multidrug-resistant tuberculosis MDR-TB and extensively drug-resistant tuberculosis XDR-TB. For an effective disease management strategy, it is crucial to understand the dynamics of T.B. infection and the impacts of treatment. In the present article, we employ AI-based machine learning techniques to investigate the immunity impact of medications. SEIPR epidemiological model is incorporated with MDR-TB for compartments susceptible to disease, exposed to risk, infected ones, preventive or resistant to initial treatment, and recovered or healed population. These

masses' natural trends, effects, and interactions are formulated and described in the present study. Computations and stability analysis are conducted upon endemic and disease-free equilibria in the present model for their global scenario. Both numerical and AI-based nonlinear autoregressive exogenous NARX analyses are presented with incorporating immediate treatment and delay in treatment. This study shows that the active patients and MDR-TB, both strains, exist because of the absence of permanent immunity to T.B. Furthermore, patients who have recovered from tuberculosis may become susceptible again by losing their immunity and contributing to transmission again. This article aims to identify patterns and predictors of treatment success. The findings from this research can contribute to developing more effective tuberculosis interventions.

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Recent TB News:

1. **WHO releases new report addressing TB among refugees and migrants**

   https://www.who.int/news/item/19-11-2024-who-releases-new-report-addressing-tb-among-refugees-and-migrants

   The WHO published a new report addressing heightened risk of contracting and difficulties with testing and treating TB for refugees and migrants. They addressed barriers and stigmas that prevented access and called for policy changes. In particular, they highlighted ten key points: mobilize political leadership, secure adequate resources, protect legal rights access care, strengthen multisectoral collaboration, enhance cross border initiatives, leverage technical guidance, empower civil society, improve surveillance, intensify targeted research , and monitor progress.

2. **Inclusion for every child: reaching every child affected by tuberculosis**

   https://www.who.int/news/item/20-11-2024-inclusion-for-every-child--reaching-every-child-affected-by-tuberculosis

   Only 3850 out of an estimated 30,000 children and adolescents with MDR TB were diagnosed and treated in 2023. The treatment outcomes in children remind strong, with over 90% of children placed on treatment having a positive outcome. For World Children's Day, the WHO reviewed their roadmap to ending TB in children and adolescents which calls for greater inclusion of children and adolescents.

3. **Breakthrough Research Promises Shorter Treatment for Multi-Drug-Resistant TB**

   https://healthpolicy-watch.news/breakthrough-research-promises-shorter-treatment-for-multi-drug-resistant-tb/

   The positive EndTB-Q trial results were shared at the Union conference. They showed that a BCDL regimen is successful in treating less severe MDR TB in 6-9 months, when compared to the longer WHO regimen. The longer WHO regimen still remains more successful in severe cases.