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1. Unlocking Opportunities for Mycobacterium leprae and Mycobacterium ulcerans.

ACS Infect Dis. 2024 Feb 9;10(2):251-269. doi: 10.1021/acsinfecdis.3c00371. Epub 2024 Jan 31.

Shyam M(1), Kumar S(2), Singh V(2)(3)(4).

In the recent decade, scientific communities have toiled to tackle the emerging burden of drug-resistant tuberculosis (DR-TB) and rapidly growing opportunistic nontuberculous mycobacteria (NTM). Among these, two neglected mycobacteria species of the Acinetobacter family, Mycobacterium leprae and Mycobacterium ulcerans, are the etiological agents of leprosy and Buruli ulcer infections, respectively, and fall under the broad umbrella of neglected tropical diseases (NTDs). Unfortunately, lackluster drug discovery efforts have been made against these pathogenic bacteria in the recent decade, resulting in the discovery of only a few countable hits and majorly repurposing anti-TB drug candidates such as telacebec (Q203), P218, and TB47 for current therapeutic interventions. Major ignorance in drug candidate identification might aggravate the dramatic consequences of rapidly spreading mycobacterial NTDs in the coming days. Therefore, this Review focuses on an up-to-date account of drug discovery efforts targeting selected druggable targets from both bacilli, including the accompanying challenges that have been identified and are responsible for the slow drug discovery. Furthermore, a succinct discussion of the all-new possibilities that could be alternative solutions to mitigate the neglected mycobacterial NTD burden and subsequently accelerate the drug discovery effort is also included. We anticipate that the state-of-the-art strategies discussed here may attract major attention from the scientific community to navigate and expand the roadmap for the discovery of next-generation therapeutics against these NTDs.

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

2. Omadacycline pharmacokinetics/pharmacodynamics and efficacy against multidrug-resistant Mycobacterium tuberculosis in the hollow fiber system model.

Antimicrob Agents Chemother. 2024 Feb 7;68(2):e0108023. doi: 10.1128/aac.01080-23. Epub 2023 Dec 22.

Singh S(1), Gumbo T(2)(3), Boorgula GD(1), Thomas TA(4), Philley JV(5), Srivastava S(1)(6).

Seventy-five years ago, first-generation tetracyclines demonstrated limited efficacy in the treatment of tuberculosis but were more toxic than efficacious. We performed a series of pharmacokinetic/pharmacodynamic (PK/PD) experiments with a potentially safer third-generation tetracycline, omadacycline, for the treatment of multidrug-resistant tuberculosis (MDR-TB). Mycobacterium tuberculosis (Mtb) H37Rv and an MDR-TB clinical strain (16D) were used in the minimum inhibitory concentration (MIC) and static concentration-response studies in test tubes, followed by a PK/PD study using the hollow fiber system model of TB (HFS-TB) that examined six human-like omadacycline doses. The inhibitory sigmoid maximal effect (Emax) model and Monte Carlo experiments (MCEs) were used for data analysis and clinical dose-finding, respectively. The omadacycline MIC for both Mtb H37Rv and MDR-TB clinical strain was 16 mg/L but dropped to 4 mg/L with daily drug supplementation to account for omadacycline degradation. The Mycobacteria Growth Indicator Tube MIC was 2 mg/L. In the test tubes, omadacycline killed 4.39 log10 CFU/mL in 7 days. On Day 28 of the HFS-TB study, the Emax was 4.64 log10 CFU/mL, while exposure mediating 50% of Emax (EC50) was an area under the concentration-time curve to MIC (AUC0-24/MIC) ratio of 22.86. This translates to PK/PD optimal exposure or EC80 as AUC0-24/MIC of 26.93. The target attainment probability of the 300-mg daily oral dose was 90% but fell at MIC ≧4 mg/L. Omadacycline demonstrated efficacy and potency against both drug-susceptible and MDR-TB. Further studies are needed to identify the omadacycline effect in combination therapy for the treatment of both drug-susceptible and MDR-TB.

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PMID: 38131673 [Indexed for MEDLINE]

Conflict of interest statement: T.G. founded and is the president and CEO of Praedicare Inc., a system of systems drug development company, and founded Praedicare Africa, a clinical contract research organization. J.V.P. is an advisor for Insmed, Paratek, and AN2 and a research investigator for Insmed, Paratek, AN2, and Zambon. All other authors have nothing to declare.

3. Determinants of drug-resistant tuberculosis in Hunan province, China: a case-control study.

BMC Infect Dis. 2024 Feb 13;24(1):198. doi: 10.1186/s12879-024-09106-5.

Akalu TY(1)(2)(3), Clements ACA(4)(5), Xu Z(6), Bai L(7), Alene KA(8)(4).

BACKGROUND: Drug-resistant tuberculosis (DR-TB) is a major public health threat in Hunan Province, with an increasing clinical burden in recent years. This study aimed to identify socio-demographic and clinical factors associated with DR-TB in Hunan province, China.
METHODS: A case-control study was conducted in Hunan province. Cases were all DR-TB patients who were confirmed by culture and Drug susceptibility testing (DST) and enrolled at the DR-TB treatment center of Hunan Chest Hospital from 2013 to 2018. Controls were all Drug Susceptible TB (DS-TB) patients confirmed by DST and enrolled at the same hospital during the same period. A multivariable logistic regression model was fitted to identify factors significantly associated with DR-TB.
RESULTS: A total of 17,808 patients (15,534 DS-TB controls and 2274 DR-TB cases) were included in the study, with a mean age of 42.5 years (standard deviation (SD) ± 17.5 years) for cases and 46.1 years (SD ± 19.1 years) for controls. Age 15-64 years (Adjusted odds ratio (AOR = 1.5, 95% CI; 1.4, 1.8)), ethnic minorities (AOR = 1.5; 95% CI; 1.4, 1.8), and a history of previous TB treatment (AOR) = 1.84; 95% CI: 1.57, 2.15) was significantly associated with DR-TB. Being resident in a province outside Hunan was also a significant risk factor (AOR = 1.67; 1.27, 2.21) for DR-TB.
CONCLUSION AND RECOMMENDATIONS: To prevent the occurrence of DR-TB in Hunan Province, interventions should be targeted at high-risk demographic groups such as ethnic minorities, individuals of productive age, and residents living outside the province. Interventions must also be targeted to previously treated cases, suggesting the appropriateness of diagnosis, treatment, and follow-up. Understanding the risk factors at the province level helps design strategies for controlling DR-TB due to variations by socioeconomic differences, quality of health care, and healthcare access.

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PMCID: PMC10863170
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Conflict of interest statement: The authors declare no competing interests.

4. Effectiveness and safety of tuberculosis preventive treatment for contacts of patients with multidrug-resistant tuberculosis: a systematic review and meta-analysis.

Clin Microbiol Infect. 2024 Feb;30(2):189-196. doi: 10.1016/j.cmi.2023.09.015. Epub 2023 Sep 22.

Zhou G(1), Luo S(2), He J(3), Chen N(4), Zhang Y(4), Cai S(5), Guo X(5), Chen H(3), Song C(6).

BACKGROUND: Contacts of patients with multidrug-resistant tuberculosis (MDR-TB) are at risk of developing TB disease. Tuberculosis preventive treatment (TPT) is an intervention that can potentially reduce this risk.
OBJECTIVES: To evaluate the effectiveness and safety of TPT for contacts of patients with MDR-TB.
DATA SOURCES: EMBASE, PubMed, Web of Science, and the Cochrane Library were searched for eligible studies on 24 July 2023, without start date restrictions.
STUDY ELIGIBILITY CRITERIA: We included studies that compared TPT with no treatment in contacts of patients with MDR-TB and reported outcomes of progression to TB disease.
PARTICIPANTS: Contacts of patients with MDR-TB.
INTERVENTIONS: TPT.
ASSESSMENT OF RISK OF BIAS: A modified version of the Newcastle-Ottawa Scale was used.
METHODS OF DATA SYNTHESIS: Random-effects meta-analysis was utilized to calculate the relative risk for disease progression to TB in contacts of patients with MDR-TB who received TPT compared to those who did not. Additionally, completion, adverse effect, and discontinued rates were assessed.
RESULTS: Involving 1105 individuals from 11 studies, the pooled relative risk for disease progression in contacts receiving TPT versus those without treatment was 0.34 (95% CI: 0.16-0.72). Subgroup analysis indicated a lower pooled relative risk for regimens based on the drug-resistance profile of the index patients with TB compared to uniform treatment regimens (0.22 [95% CI: 0.06-0.84] vs. 0.49 [95% CI: 0.17-1.35]), although not statistically significant. The pooled completed rate was 83.8%, adverse effect rate was 22.9%, and discontinued rate was 6.5%. After excluding the levofloxacin and pyrazinamide regimen study, the completed rate increased to 88.0%, and adverse effects and discontinued rates decreased to 8.0% and 4.0%, respectively.
DISCUSSION: TPT reduces TB disease progression risk in contacts of patients with MDR-TB. Tailored TPT regimens based on drug-resistance profiles may offer additional benefits. Furthermore, efforts to improve completed rates and manage adverse effects are essential for optimizing effectiveness and safety.

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PMID: 37741621 [Indexed for MEDLINE]

5. Short oral regimens for pulmonary rifampicin-resistant tuberculosis (TB-PRACTECAL): an open-label, randomised, controlled, phase 2B-3, multi-arm, multicentre, non-inferiority trial.

Lancet Respir Med. 2024 Feb;12(2):117-128. doi: 10.1016/S2213-2600(23)00389-2. Epub 2023 Nov 16.

Nyang'wa BT(1), Berry C(2), Kazounis E(2), Motta I(2), Parpieva N(3), Tigay Z(4), Moodliar R(5), Dodd M(6), Solodovnikova V(7), Liverko I(3), Rajaram S(8), Rassool M(8), McHugh T(9), Spigelman M(10), Moore DA(6), Ritmeijer K(11), du Cros P(12), Fielding K(6); TB-PRACTECAL team.

Collaborators: Da Costa E, Lachenal N, James N, Sinha A, LeBeau K, Douch E, Jolivert P, Poulsom H, Conijn M, King S, Spencer H, Cunden E, Batts C, Vuong T, Dietrich S, McRae M, Wong S, Sun E, Olugbosi M, Shanks L, Hughes M, Nahid P, Kumwenda J, Lorenz T, Majumdar S, Horsburgh RC, Nuermberger E, Meintjes G, Eisenach K, Lienhardt C, Nunn A, Lange C, Park L, Gatts C, Warren D, Kleiman R, Mokua Nyangweso G, Ochieng M, Egondi T, Onyango K, Omollo T, Omollo R, Sturgess J, Saunders S, Allen E, Gajewski S, Butoescu V, Hanekova J, Etter C, Kambarov Y, Mphele S, Sukhinina V, Huzar O, Reshetnikov A, Cilliè C, Ahmed N, Hunt R, Merle C, Gulayim A, Mbenga M, Baltasheva ZS, Abdrasuliev T, Margaryan H, Urgenishbaevna UG, Skrahina A, Yatskevich N, Viatushka D, Apanasevich T, Skrahin A, Duckworth L, Narasimooloo C, Lesego NE, Motlhako S, Mashamaite ME, Mojapelo E.

BACKGROUND: Around 500 000 people worldwide develop rifampicin-resistant tuberculosis each year. The proportion of successful treatment outcomes remains low and new treatments are needed. Following an interim analysis, we report the final safety and efficacy outcomes of the TB-PRACTECAL trial, evaluating the safety and efficacy of oral regimens for the treatment of rifampicin-resistant tuberculosis.
METHODS: This open-label, randomised, controlled, multi-arm, multicentre, non-inferiority trial was conducted at seven hospital and community sites in Uzbekistan, Belarus, and South Africa, and enrolled participants aged 15 years and older with pulmonary rifampicin-resistant tuberculosis. Participants were randomly assigned, in a 1:1:1:1 ratio using variable block randomisation and stratified by trial site, to receive 36-80 week standard care; 24-week oral bedaquiline, pretomanid, and linezolid (BPaL); BPaL plus clofazimine (BPaLC); or BPaL plus moxifloxacin (BPaLM) in stage one of the trial, and in a 1:1 ratio to receive standard care or BPaLM in stage two of the trial, the results of which are described here. Laboratory staff and trial sponsors were masked to group assignment and outcomes were assessed by unmasked investigators. The primary

outcome was the percentage of participants with a composite unfavourable outcome (treatment failure, death, treatment discontinuation, disease recurrence, or loss to follow-up) at 72 weeks after randomisation in the modified intention-to-treat population (all participants with rifampicin-resistant disease who received at least one dose of study medication) and the per-protocol population (a subset of the modified intention-to-treat population excluding participants who did not complete a protocol-adherent course of treatment (other than because of treatment failure or death) and those who discontinued treatment early because they violated at least one of the inclusion or exclusion criteria). Safety was measured in the safety population. The non-inferiority margin was 12%. This trial is registered with ClinicalTrials.gov, NCT02589782, and is complete.
FINDINGS: Between Jan 16, 2017, and March 18, 2021, 680 patients were screened for eligibility, of whom 552 were enrolled and randomly assigned (152 to the standard care group, 151 to the BPaLM group, 126 to the BPaLC group, and 123 to the BPaL group). The standard care and BPaLM groups proceeded to stage two and are reported here, post-hoc analyses of the BPaLC and BPaL groups are also reported. 151 participants in the BPaLM group and 151 in the standard care group were included in the safety population, with 138 in the BPaLM group and 137 in the standard care group in the modified intention-to-treat population. In the modified intention-to-treat population, unfavourable outcomes were reported in 16 (12%) of 137 participants for whom outcome was assessable in the BPaLM group and 56 (41%) of 137 participants in the standard care group (risk difference -29·2 percentage points [96·6% CI -39·8 to -18·6]; non-inferiority and superiority p<0·0001). 34 (23%) of 151 participants receiving BPaLM had adverse events of grade 3 or higher or serious adverse events, compared with 72 (48%) of 151 participants receiving standard care (risk difference -25·2 percentage points [96·6% CI -36·4 to -13·9]). Five deaths were reported in the standard care group by week 72, of which one (COVID-19 pneumonia) was unrelated to treatment and four (acute pancreatitis, suicide, sudden death, and sudden cardiac death) were judged to be treatment-related.
INTERPRETATION: The 24-week, all-oral BPaLM regimen is safe and efficacious for the treatment of pulmonary rifampicin-resistant tuberculosis, and was added to the WHO guidance for treatment of this condition in 2022. These findings will be key to BPaLM becoming the preferred regimen for adolescents and adults with pulmonary rifampicin-resistant tuberculosis.
FUNDING: Médecins Sans Frontières.

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PMID: 37980911 [Indexed for MEDLINE]

Conflict of interest statement: Declaration of interests B-TN, CB, EK, and IM are employees of Médecins Sans Frontières. MR participates on the data safety monitoring board for the BEAT-TB trial (NCT04062201). PdC is a former employee of Médecins Sans Frontières and received consultancy fees and conference attendance support from the organisation between 2020 and 2022. He has also received grants from the Department of Foreign Affairs and Trade and the Medical Research Future Fund of the Australian Government; FIND; the Global Fund to Fight AIDS, Tuberculosis and Malaria; and STOP TB; and honoraria for training sessions from the regional Green Light Committee (Western Pacific Regional Office), of which he is an unpaid committee member. TM has received grants from the Global Alliance Against Tuberculosis, the European & Developing Countries Clinical Trials Partnership, and the EU Innovative Medicines Initiative; is co-editor in chief of Annals of Clinical Microbiology and Antimicrobials (Springer Nature); and is the chair of the Acid Fast Club (unpaid). MD and KF received salary funding paid to the London School of Hygiene & Tropical Medicine (London, UK) by Médecins Sans Frontières. All other authors declare no competing interests.

6. TB-DROP: deep learning-based drug resistance prediction of Mycobacterium tuberculosis utilizing whole genome mutations.

BMC Genomics. 2024 Feb 12;25(1):167. doi: 10.1186/s12864-024-10066-y.

Wang Y(1), Jiang Z(2), Liang P(2)(3), Liu Z(2), Cai H(4), Sun Q(5).

The most widely practiced strategy for constructing the deep learning (DL) prediction model for drug resistance of Mycobacterium tuberculosis (MTB) involves the adoption of ready-made and state-of-the-art architectures usually proposed for non-biological problems. However, the ultimate goal is to construct a customized model for predicting the drug resistance of MTB and eventually for the biological phenotypes based on genotypes. Here, we constructed a DL training framework to standardize and modularize each step during the training process using the latest tensorflow 2 API. A systematic and comprehensive evaluation of each module in the three currently representative models, including Convolutional Neural Network, Denoising Autoencoder, and Wide & Deep, which were adopted by CNNGWP, DeepAMR, and WDNN, respectively, was performed in this framework regarding module contributions in order to assemble a novel model with proper dedicated modules. Based on the whole-genome level mutations, a de novo learning method was developed to overcome the intrinsic limitations of previous models that rely on known drug resistance-associated loci. A customized DL model with the multilayer perceptron architecture was constructed and achieved a competitive performance (the mean sensitivity and specificity were 0.90 and 0.87, respectively) compared to previous ones. The new model developed was

applied in an end-to-end user-friendly graphical tool named TB-DROP (TuBerculosis Drug Resistance Optimal Prediction: https://github.com/nottwy/TB-DROP), in which users only provide sequencing data and TB-DROP will complete analysis within several minutes for one sample. Our study contributes to both a new strategy of model construction and clinical application of deep learning-based drug-resistance prediction methods.

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PMCID: PMC10860279
PMID: 38347478 [Indexed for MEDLINE]

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

7. Genomic analysis of lineage-specific transmission of multidrug resistance tuberculosis in China.

Emerg Microbes Infect. 2024 Dec;13(1):2294858. doi: 10.1080/22221751.2023.2294858. Epub 2024 Feb 13.

Li YF(1), Kong XL(2), Song WM(3), Li YM(4)(5), Li YY(4)(5), Fang WW(4), Yang JY(4), Yu CB(6), Li HC(4), Liu Y(4).

OBJECTIVES: We investigated the genetic diversities and lineage-specific transmission dynamics of multidrug-resistant tuberculosis (MDR-TB), with the goal of determining the potential factors driving the MDR epidemics in China.
METHODS: We curated a large nationwide Mycobacterium tuberculosis (M. tuberculosis) whole genome sequence data set, including 1313 MDR strains. We reconstructed the phylogeny and mapped the transmission networks of MDR-TB across China using Bayesian inference. To identify drug-resistance variants linked to enhanced transmissibility, we employed ordinary least-squares (OLS) regression analysis.
RESULT: The majority of MDR-TB strains in China belong to lineage 2.2.1. Transmission chain analysis has indicated that the repeated and frequent transmission of L2.2.1 plays a central role in the establishment of MDR epidemic in China, but no occurrence of a large predominant MDR outbreak was detected. Using OLS regression, the most common single nucleotide polymorphisms (SNPs) associated with resistance to isoniazid (katG_p.Ser315Thr and katG_p.Ser315Asn) and rifampicin (rpoB_p.Ser450Leu, rpoB_p.His445Tyr, rpoB_p.His445Arg, rpoB_p.His445Asp, and rpoB_p.His445Asn) were more likely to be found in L2 clustered strains. Several putative compensatory mutations in rpoA, rpoC, and katG were significantly associated with clustering. The eastern, central, and

southern regions of China had a high level of connectivity for the migration of L2 MDR strains throughout the country. The skyline plot showed distinct population size expansion dynamics for MDR-TB lineages in China.
CONCLUSION: MDR-TB epidemic in China is predominantly driven by the spread of highly transmissible Beijing strains. A range of drug-resistance mutations of L2 MDR-TB strains displayed minimal fitness costs and may facilitate their transmission.

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PMCID: PMC10866052
PMID: 38126135 [Indexed for MEDLINE]

Conflict of interest statement: No potential conflict of interest was reported by the author(s).

8. Prevalence, Transmission and Genetic Diversity of Pyrazinamide Resistance Among Multidrug-Resistant Mycobacterium tuberculosis Isolates in Hunan, China.

Infect Drug Resist. 2024 Feb 1;17:403-416. doi: 10.2147/IDR.S436161. eCollection 2024.

Liu B(#)(1), Su P(#)(1), Hu P(#)(1), Yan M(1), Li W(1), Yi S(1), Chen Z(1), Zhang X(1), Guo J(1), Wan X(1), Wang J(1), Gong D(1), Bai H(1), Wan K(2), Liu H(2), Li G(2), Tan Y(1).

BACKGROUND: China is a country with a burden of high rates of both TB and multidrug-resistant TB (MDR-TB). However, published data on pyrazinamide (PZA) resistance are still limited in Hunan province, China. This study investigated the prevalence, transmission, and genetic diversity of PZA resistance among multidrug-resistant Mycobacterium tuberculosis isolates in Hunan province.
METHODS: Drug susceptibility testing (DST) with the Bactec MGIT 960 PZA kit and pyrazinamidase (PZase) testing were conducted on all 298 MDR clinical isolates. Moreover, 24-locus MIRU-VNTR and DNA sequencing of pncA, rpsA, and panD genes were conducted on 180 PZA-resistant (PZA-R) isolates.
RESULTS: The prevalence of PZA resistance among MDR-TB strains reached 60.4%. Newly diagnosed PZA-R TB patients and clustered isolates with identical pncA, rpsA, and panD mutations showed that transmission of PZA-R isolates played a significant role in the formation of PZA-R TB. Ninety-eight mutation patterns were observed in the pncA among 180 PZA-R isolates, and seventy-one (72.4%) were point mutations. Twenty-four of these mutations are new, including 2 base substitutions (V93G and T153S) and 22 nucleotide deletions or insertions. The W119C was found in PZA-S isolates, on the other hand, F94L and V155A mutations were found in both PZA resistant and susceptible isolates with positive PZase activity, indicating that they were not associated with PZA resistance. This is

not entirely in line with the WHO catalogue. Ten novel rpsA mutations were found in 10 PZA-R isolates, which all combined with mutations in pncA. Thus, it is unpredictable whether these mutations in rpsA can impact PZA resistance. No panD mutation was found in all PZA-R isolates.
CONCLUSION: DNA sequencing of pncA and PZase activity testing have great potential in predicting PZA resistance.

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PMCID: PMC10849141
PMID: 38328339

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

9. Efficacy and safety of bedaquiline containing regimens in patients of drug-resistant tuberculosis: An updated systematic review and meta-analysis.

J Clin Tuberc Other Mycobact Dis. 2023 Dec 1;34:100405. doi: 10.1016/j.jctube.2023.100405. eCollection 2024 Feb.

Ur Rehman O(1), Fatima E(1), Ali A(2), Akram U(3), Nashwan A(4), Yunus F(5).

BACKGROUND: Tuberculosis is an infectious disease caused by Mycobacterium tuberculosis and leads to serious complications if left untreated. Some strains of Mycobacterium tuberculosis are multi-drug resistant and require treatment with newer drugs. Bedaquiline based treatment regimens have been used in patients who are diagnosed with drug resistant tuberculosis. The aim of this study is to assess the efficacy and safety profile of bedaquiline-based treatment regimens using a systematic review of existing literature and meta-analysis.
METHODS: In this study, an electronic search was carried out on PubMed, ScienceDirect, and Cochrane library to find relevant literature from March 2021 onwards. Random-effects model was used to assess pooled treatment success rate and 95 % CIs. p-value of <0.05 was suggestive of publication bias. The review is registered with PROSPERO: CRD42023432748.
RESULTS: A total of 543 articles were retrieved by database searching, out of which 12 new studies met the inclusion criteria. The total number of articles included in the review was 41 including 36 observational studies (having a total of 9,934 patients) and 5 experimental studies (having a total of 468 patients). The pooled treatment success rate was 76.9 % (95 % CI, 72.9-80.4) in the observational studies and 81.7 % (95 % CI, 67.2-90.7) in the experimental

studies. Further subgroup analysis was done on the basis of treatment regimens containing bedaquiline only and treatment regimens containing bedaquiline and delamanid. The pooled treatment success rate in the studies consisting of patients who were treated with regimens containing bedaquiline only was 78.4 % (95 % CI, 74.2-82.1) and 73.6 % (95 % CI, 64.6-81.0) in studies consisting of patients who were treated with regimens containing bedaquiline and delamanid. There was no evidence of publication bias.
CONCLUSIONS: In patients of drug resistant tuberculosis having highly resistant strains of Mycobacterium tuberculosis undergoing treatment with bedaquiline-based regimen demonstrate high rates of culture conversion and treatment success. Moreover, the safety profile of bedaquiline-based regimens is well-established in all studies.

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PMCID: PMC10750101
PMID: 38152568

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.

10. Prevalence of Rifampicin resistance tuberculosis among presumptive tuberculosis patients in Egypt-2021: a national health facility-based survey.

BMC Infect Dis. 2024 Feb 15;24(1):210. doi: 10.1186/s12879-023-08807-7.

Amin W(1), Gadallah M(2), Salah A(3), Rady M(4).

BACKGROUND: The magnitude of MDR-TB cases was noticeable in Egypt. However, the last national survey was 11-years ago. The current survey was conducted to determine the prevalence of rifampicin resistance among sputum smear-positive pulmonary tuberculosis patients in Egypt.
METHODS: A national health facility-based cross-sectional study was conducted in 14 randomly selected governorates in Egypt between August 2020 and September 2021. All presumptive TB cases, either new or previously treated according to WHO definitions, with no gender, age, or nationality limitations, and provided informed consent were included in the study. Each patient completed a case report form (CRF). The CRF included socio-demographic and clinical data. Sputum samples were collected according to standard techniques and cultured on Lowenstein-Jensen (L-J) medium. Gene X-pert test was carried out first on the samples for simultaneous identification of MTB and rifampicin resistance. The prevalence of RR was calculated using crude, cluster, and weighted methods.

Factors associated with RR were analyzed by bivariate and multivariate techniques.
RESULTS: Among the total 849 presumptive TB patients enrolled in the study, 710 (83.6%) patients were subjected to Gene X-pert testing (MTB/RIF). The crude prevalence of RR was 3.32% (95% CI: 1.89-4.76%) among the new cases and 9.46% (95% CI: 2.63-16.29%) among the retreated cases with an overall estimate of 3.99%; (95% CI: 2.51-5.47%). By cluster analysis the overall prevalence of RR was 5.01% (95% CI: 2.90-7.13). Factors associated with the prevalence of RR were co-morbidity with bronchial asthma, drug abuse and history of contact with a family member with TB.
CONCLUSION: The prevalence of RR among either new or retreated cases TB patients was lower than the previous Egyptian rates in 2010-2012. The strongest predictor associated with RR was comorbidity with bronchial asthma.

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PMCID: PMC10870666
PMID: 38360617 [Indexed for MEDLINE]

Conflict of interest statement: We declare that potential conflict of interest does not exist. The authors declare no competing interests.

11. On the onset and dispersal of a major MDR TB clone among HIV-negative patients, Tunisia.

Antimicrob Resist Infect Control. 2024 Feb 14;13(1):18. doi: 10.1186/s13756-023-01360-7.

Dekhil N(1), Mardassi H(2).

BACKGROUND: To carry out a whole genome sequencing (WGS)-based investigation on the emergence and spread of the largest multidrug-resistant tuberculosis (MDR TB) outbreak that has been thriving among HIV-negative patients, Tunisia, since the early 2000s.
METHODS: We performed phylogeographic analyses and molecular dating based on a WGS dataset representing 68 unique Mycobacterium tuberculosis isolates, covering almost the entire MDR TB outbreak for the time period 2001-2016.
RESULTS: The data indicate that the ancestor of the MDR TB outbreak emerged in the region of Bizerte, as early as 1974 (95% CI 1951-1985), from where it spread to other regions by 1992 (95% CI 1980-1996). Analysis of a minimum spanning tree based on core genome Multilocus Sequence Typing (cgMLST) uncovered the early spill-over of the fitness-compensated MDR TB strain from the prison into the general population. Indeed, cases with history of incarceration were found to be

directly or indirectly linked to up to 22 new outbreak cases (32.35%) among the non-imprisoned population. By around 2008, the MDR TB outbreak strain had acquired additional resistance, leading to an XDR phenotype.
CONCLUSIONS: WGS allowed refining our understanding of the emergence and evolution of the largest MDR TB outbreak in Tunisia, whose causative strain has been circulating silently for almost 26 years before. Our study lends further support to the critical role of prisons-related cases in the early spread of the outbreak among the general population. The shift to an XDR phenotype of such an epidemic clone prompts an urgent need to undertake drastic control measures.

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

12. A spotlight on the tuberculosis epidemic in South Africa.

Nat Commun. 2024 Feb 12;15(1):1290. doi: 10.1038/s41467-024-45491-w.

[No authors listed]

Tuberculosis is the leading cause of death from a single infectious agent, with over 25% of these occurring in the African region. Multi-drug resistant strains which do not respond to first-line antibiotics continue to emerge, putting at risk numerous public health strategies which aim to reduce incidence and mortality. Here, we speak with Professor Valerie Mizrahi, world-leading researcher and former director of the Institute of Infectious Disease and Molecular Medicine at the University of Cape Town, regarding the tuberculosis burden in South Africa. We discuss the challenges faced by researchers, the lessons that need to be learnt and current innovations to better understand the overall response required to accelerate progress.

DOI: 10.1038/s41467-024-45491-w
PMCID: PMC10861440
PMID: 38346962 [Indexed for MEDLINE]

13. Risk factors for diagnosis and treatment delay among patients with multidrug-resistant tuberculosis in Hunan Province, China.

BMC Infect Dis. 2024 Feb 2;24(1):159. doi: 10.1186/s12879-024-09036-2.

Akalu TY(1)(2)(3), Clements ACA(4)(5), Gebreyohannes EA(4)(6), Xu Z(7), Bai L(8), Alene KA(9)(4)(10).

BACKGROUND: Multidrug-resistant tuberculosis (MDR-TB) is a global health threat associated with high morbidity and mortality rates. Diagnosis and treatment delays are associated with poor treatment outcomes in patients with MDR-TB. However, the risk factors associated with these delays are not robustly investigated, particularly in high TB burden countries such as China. Therefore, this study aimed to measure the length of diagnosis and treatment delays and identify their risk factors among patients with MDR-TB in Hunan province.
METHODS: A retrospective cohort study was conducted using MDR-TB data from Hunan province between 2013 and 2018. The main outcomes of the study were diagnosis and treatment delay, defined as more than 14 days from the date of symptom to diagnosis confirmation (i.e., diagnosis delay) and from diagnosis to treatment commencement (i.e., treatment delay). A multivariable logistic regression model was fitted, and an adjusted odds ratio (AOR) with a 95% confidence interval (CI) was used to identify factors associated with diagnosis and treatment delay.
RESULTS: In total, 1,248 MDR-TB patients were included in this study. The median length of diagnosis delays was 27 days, and treatment delays were one day. The proportion of MDR-TB patients who experienced diagnosis and treatment delay was 62.82% (95% CI: 60.09-65.46) and 30.77% (95% CI: 28.27-33.39), respectively. The odds of experiencing MDR-TB diagnosis delay among patients coming through referral and tracing was reduced by 41% (AOR = 0.59, 95% CI: 0.45-0.76) relative to patients identified through consultations due to symptoms. The odds of experiencing diagnosis delay among ≥ 65 years were 65% (AOR = 0.35, 0.14-0.91) lower than under-15 children. The odds of developing treatment delay among foreign nationalities and people from other provinces were double (AOR = 2.00, 95% CI: 1.31-3.06) compared to the local populations. Similarly, the odds of experiencing treatment delay among severely ill patients were nearly 2.5 times higher (AOR = 2.49, 95% CI: 1.41-4.42) compared to patients who were not severely ill. On the other hand, previously treated TB cases had nearly 40% (AOR = 0.59, 95% CI: 0.42-0.85) lower odds of developing treatment delay compared with new MDR-TB cases. Similarly, other ethnic minority groups had nearly 40% (AOR = 0.57, 95% CI: 0.34-0.96) lower odds of experiencing treatment delay than the Han majority.
CONCLUSIONS: Many MDR-TB patients experience long diagnosis and treatment delays in Hunan province. Strengthening active case detection can significantly reduce diagnosis delays among MDR-TB patients. Moreover, giving attention to patients who are new to MDR-TB treatment, are severely ill, or are from areas outside Hunan province will potentially reduce the burden of treatment delay among MDR-TB patients.

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PMID: 38308252 [Indexed for MEDLINE]

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

14. Enhanced active case finding of drug-resistant tuberculosis in Namibia: a protocol for the hotspots, hospitals, and households (H3TB) study.

BMJ Open. 2024 Feb 10;14(2):e082665. doi: 10.1136/bmjopen-2023-082665.

Shavuka O(1), Iipumbu E(1), Boois L(1), Günther G(1)(2), Hoddinott G(3), Lin HH(4), Nepolo E(1), Niemann S(1)(5), Ruswa N(6), Seddon J(3)(7), Claassens MM(8)(3).

INTRODUCTION: Namibia is a high tuberculosis (TB)-burden country with an estimated incidence of 460/100 000 (around 12 000 cases) per year. Approximately 4.5% of new cases and 7.9% of previously treated TB cases are multidrug resistant (MDR) and 47% of patients with MDR-TB are HIV coinfected. Published data suggest a clustering of MDR-TB transmission in specific areas. Identifying transmission clusters is key to implementing high-yield and cost-effective interventions. This includes knowing the yield of finding TB cases in high-transmission zones (eg, community hotspots, hospitals or households) to deliver community-based interventions. We aim to identify such transmission zones for enhanced case finding and evaluate the effectiveness of this approach.
METHODS AND ANALYSIS: H3TB is an observational cross-sectional study evaluating MDR-TB active case finding strategies. Sputum samples from MDR-TB cases in three regions of Namibia will be evaluated by whole genome sequencing (WGS) in addition to routine sputum investigations (Xpert MTB/RIF, culture and drug susceptibility testing). We will collect information on household contacts, use of community spaces and geographical map intersections between participants, synthesising these data to identify transmission hotspots. We will look at the feasibility, acceptability, yield and cost of case finding strategies in these hotspots, and in households of patients with MDR-TB and visitors of hospitalised patients with MDR-TB. A compartmental transmission dynamic model will be constructed to evaluate the impact and cost-effectiveness of the strategies if scaled.
ETHICS AND DISSEMINATION: Ethics approval was obtained. Participants will give informed consent. H3TB will capitalise on a partnership with the Ministry of Health and Social Services to follow up individuals diagnosed with MDR-TB and

integrate WGS data with innovative contact network mapping, to allow enhanced case finding. Study data will contribute towards a systems approach to TB control. Equally important, it will serve as a role model for similar studies in other high-incidence settings.

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PMCID: PMC10862302
PMID: 38341211 [Indexed for MEDLINE]

Conflict of interest statement: Competing interests: None declared.

15. Time to sputum culture conversion and its associated factors among drug-resistant tuberculosis patients: a systematic review and meta-analysis.

BMC Infect Dis. 2024 Feb 7;24(1):169. doi: 10.1186/s12879-024-09009-5.

Wenlu Y(#)(1), Xia Z(#)(1), Chuntao W(1), Qiaolin Y(1), Xujue X(1), Rong Y(1), Dan S(2), Xi Y(2), Bin W(3).

OBJECTIVE: We aimed to evaluate the sputum culture conversion time of DR-TB patients and its related factors.
METHODS: PubMed, The Cochrane Library, Embase, CINAHL, Web of Science, CNKI, Wan Fang, CBM and VIP databases were electronically searched to collect studies on sputum culture conversion time in patients with DR-TB. Meta-analysis was performed by using the R 4.3.0 version and Stata 16 software.
RESULTS: A total of 45 studies involving 17373 patients were included. Meta-analysis results showed that the pooled median time to sputum culture conversion was 68.57 days (IQR 61.01,76.12). The median time of sputum culture conversion in patients with drug-resistant tuberculosis was different in different WHO regions, countries with different levels of development and different treatment schemes. And female (aHR = 0.59,95%CI: s0.46,0.76), alcohol history (aHR = 0.70,95%CI:0.50,0.98), smoking history (aHR = 0.58,95%CI:0.38,0.88), history of SLD use (aHR = 0.64,95%CI:0.47,0.87), BMI < 18.5 kg/m2 (aHR = 0.69,95%CI:0.60,0.80), lung cavity (aHR = 0.70,95%CI:0.52,0.94), sputum smear grading at baseline (Positive) (aHR = 0.56,95%CI:0.36,0.87), (grade 1+) (aHR = 0.87,95%CI:0.77,0.99), (grade 2+) (aHR = 0.81,95%CI:0.69,0.95), (grade 3+) (aHR = 0.71,95%CI:0.61,0.84) were the related factor of sputum culture conversion time in patients with DR-TB.
CONCLUSION: Patients with DR-TB in Europe or countries with high level of economic development have earlier sputum culture conversion, and the application of bedaquiline can make patients have shorter sputum culture conversion time.

Female, alcohol history, smoking history, history of SLD use, BMI < 18.5 kg/m2, lung cavity, sputum smear grading at baseline (Positive, grade 1+, grade 2+, grade 3+) may be risk factors for longer sputum culture conversion time. This systematic review has been registered in PROSPERO, the registration number is CRD42023438746.

DOI: 10.1186/s12879-024-09009-5
PMCID: PMC10848338
PMID: 38326758 [Indexed for MEDLINE]

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

16. Landscaping tuberculosis multimorbidity: findings from a cross-sectional study in India.

BMC Public Health. 2024 Feb 13;24(1):453. doi: 10.1186/s12889-024-17828-z.

Chauhan A(1), Parmar M(2), Rajesham JD(3), Shukla S(4), Sahoo KC(5), Chauhan S(4), Chitiboyina S(6), Sinha A(5), Srigana G(4), Gorla M(4), Pati S(7).

BACKGROUND: Multimorbidity, the concurrent presence of two or more chronic conditions is an emerging public health challenge. Till date, most of the research have focused on the presence and interaction of selected co-morbidities in tuberculosis (TB). There exist a critical knowledge gap on the magnitude of multimorbidity among TB patients and its impact on health outcomes.
METHODS: We undertook a cross-sectional study to assess the prevalence and patterns of multimorbidity among newly diagnosed TB patients in two states of India. A total of 323 patients were interviewed using a structured multimorbidity assessment questionnaire for primary care (MAQ-PC). MAQ-PC is already validated for Indian population and elicits 22 chronic conditions. We defined TB multimorbidity as the co-existence of TB with one or more chronic conditions and identified commonly occurring dyads (TB + single condition) and triads (TB + two conditions).
RESULTS: More than half (52%) of TB patients reported multimorbidity. Among dyads, depression, diabetes mellitus (DM), acid peptic disease (APD), hypertension, chronic alcoholism, arthritis and chronic back ache (CBA) were the most common co-occurring conditions while 'DM + arthritis', 'depression + APD', 'depression + DM' were the most commonly occurring triads among TB patients. Factors such as increasing age, low levels of education, alcohol abusers, drug-resistant TB and having health insurance were significantly associated with multimorbidity among TB patients.

CONCLUSIONS: Our findings suggest high prevalence of multimorbidity among newly diagnosed TB patients in India. The presence of concordant and discordant conditions with TB may increase the health complexity, thus necessitating appropriate care protocols. Given, the current situation, wherein TB and non-communicable diseases (NCD) services are delivered through collaborative framework between programmes, there is a need for addressing multimorbidity at the healthcare delivery level.

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PMCID: PMC10863254
PMID: 38350875 [Indexed for MEDLINE]

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

17. Identification and optimization of pyridine carboxamide-based scaffold as a drug lead for Mycobacterium tuberculosis.

Antimicrob Agents Chemother. 2024 Feb 7;68(2):e0076623. doi: 10.1128/aac.00766-23. Epub 2024 Jan 9.

Singh P(#)(1), Kumar A(#)(1), Sharma P(1), Chugh S(1), Kumar A(2), Sharma N(1), Gupta S(1), Singh M(1), Kidwai S(1), Sankar J(1), Taneja N(1), Kumar Y(1), Dhiman R(2), Mahajan D(1), Singh R(1).

New drugs with novel mechanisms of action are urgently needed to tackle the issue of drug-resistant tuberculosis. Here, we have performed phenotypic screening using the Pathogen Box library obtained from the Medicines for Malaria Venture against Mycobacterium tuberculosis in vitro. We have identified a pyridine carboxamide derivative, MMV687254, as a promising hit. This molecule is specifically active against M. tuberculosis and Mycobacterium bovis Bacillus Calmette-Guérin (M. bovis BCG) but inactive against Enterococcus faecalis, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumanii, Pseudomonas aeruginosa, and Escherichia coli pathogens. We demonstrate that MMV687254 inhibits M. tuberculosis growth in liquid cultures in a bacteriostatic manner. Surprisingly, MMV687254 was as active as isoniazid in macrophages and inhibited M. tuberculosis growth in a bactericidal manner. Mechanistic studies revealed that MMV687254 is a prodrug and that its anti-mycobacterial activity requires AmiC-dependent hydrolysis. We further demonstrate that MMV687254 inhibits M. tuberculosis growth in macrophages by inducing autophagy. In the present study, we have also carried out a detailed structure-activity relationship study and identified a promising novel lead candidate. The

identified novel series of compounds also showed activity against drug-resistant M. bovis BCG and M. tuberculosis clinical strains. Finally, we demonstrate that in contrast to MMV687254, the lead molecule was able to inhibit M. tuberculosis growth in a chronic mouse model of infection. Taken together, we have identified a novel lead molecule with a dual mechanism of action that can be further optimized to design more potent anti-tubercular agents.

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PMCID: PMC10848774
PMID: 38193667 [Indexed for MEDLINE]

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

18. Low body mass index as a predictor of sputum culture conversion and treatment outcomes among patients receiving treatment for multidrug-resistant tuberculosis in Lesotho.

Glob Health Action. 2024 Dec 31;17(1):2305930. doi: 10.1080/16549716.2024.2305930. Epub 2024 Feb 2.

Oyewusi L(1), Zeng C(2), Seung KJ(3), Mpinda S(1), Kunda M(1), Mitnick CD(2), Kanu M(1), Tamirat M(1), Makaka J(1), Mofolo M(1), Maime R(1), Maama L(4), Senyo N(1), Oguntoyinbo B(1), Mayombo L(1), Franke MF(2).

BACKGROUND: A low body mass index (BMI) at the start of treatment for rifampicin- or multidrug-resistant tuberculosis (MDR/RR-TB) is associated with poor treatment outcomes and may contribute to delayed sputum culture conversion, thereby prolonging the period of potential transmission to others. Whether the relative importance of low BMI in predicting treatment outcomes differs by HIV status is unclear.
OBJECTIVES: We evaluated the association between low BMI and two dependent variables, sputum culture conversion and end-of-treatment outcome, among patients receiving treatment for MDR/RR-TB in Lesotho, a setting with a high prevalence of HIV infection.
METHODS: Secondary data from a prospective cohort of patients initiating a longer (18-20 months) treatment containing bedaquiline and/or delamanid under routine programmatic conditions in Lesotho were analysed. Risk ratios and differences were adjusted for potential confounders using multivariable logistic regression, and estimates were stratified by HIV status.
RESULTS: Of 264 patients, 105 and 250 were eligible for culture conversion and end-of-treatment analyses, respectively. Seventy-one per cent of patients (74/105) experienced culture conversion within six months, while 74% (184/250) experienced a favourable end-of-treatment outcome. Low BMI was associated with a lower frequency of culture conversion at six months among those who were not

living with HIV (relative risk [RR]: 0.50 [95% CI: 0.21, 0.79]); this association was attenuated among those living with HIV (RR: 0.88 [95% CI: 0.68, 1.23]). A low BMI was moderately associated with a lower frequency of treatment success (RR = 0.89 [95% CI: 0.77, 1.03]), regardless of HIV status.
CONCLUSIONS: Low BMI was common and associated with the frequency of six-month culture conversion and end-of-treatment outcomes. The association with culture conversion was more pronounced among those not living with HIV. Addressing the myriad factors that drive low BMI in this setting could hasten culture conversion and improve end-of-treatment outcomes. This will require a multipronged approach focused on alleviating food insecurity and enabling prompt diagnosis and treatment of HIV and TB.

DOI: 10.1080/16549716.2024.2305930
PMCID: PMC10840591
PMID: 38305025 [Indexed for MEDLINE]

Conflict of interest statement: No potential conflict of interest was reported by the author(s).

19. The heme oxygenase-1 metalloporphyrin inhibitor stannsoporfin enhances the bactericidal activity of a novel regimen for multidrug-resistant tuberculosis in a murine model.

Antimicrob Agents Chemother. 2024 Feb 7;68(2):e0104323. doi: 10.1128/aac.01043-23. Epub 2023 Dec 22.

Ruelas Castillo J(1), Neupane P(1), Karanika S(1), Krug S(1), Quijada D(1), Garcia A(1), Ayeh S(1), Yilma A(1), Costa DL(2)(3), Sher A(4), Fotouhi N(5), Serbina N(5), Karakousis PC(1)(6)(7).

Update of
bioRxiv. 2023 Nov 13;:

Multidrug-resistant (MDR) Mycobacterium tuberculosis (Mtb) poses significant challenges to global tuberculosis (TB) control efforts. Host-directed therapies (HDTs) offer a novel approach to TB treatment by enhancing immune-mediated clearance of Mtb. Prior preclinical studies found that the inhibition of heme oxygenase-1 (HO-1), an enzyme involved in heme metabolism, with tin-protoporphyrin IX (SnPP) significantly reduced mouse lung bacillary burden when co-administered with the first-line antitubercular regimen. Here, we evaluated the adjunctive HDT activity of a novel HO-1 inhibitor, stannsoporfin (SnMP), in combination with a novel MDR-TB regimen comprising a next-generation diarylquinoline, TBAJ-876 (S), pretomanid (Pa), and a new oxazolidinone, TBI-223

(O) (collectively, SPaO), in Mtb-infected BALB/c mice. After 4 weeks of treatment, SPaO + SnMP 5mg/kg reduced mean lung bacillary burden by an additional 0.69 log10 (P = 0.01) relative to SPaO alone. As early as 2 weeks post-treatment initiation, SnMP adjunctive therapy differentially altered the expression of pro-inflammatory cytokine genes and CD38, a marker of M1 macrophages. Next, we evaluated the sterilizing potential of SnMP adjunctive therapy in a mouse model of microbiological relapse. After 6 weeks of treatment, SPaO + SnMP 10mg/kg reduced lung bacterial burdens to 0.71 ± 0.23 log10 colony-forming units (CFUs), a 0.78 log-fold greater decrease in lung CFU compared to SpaO alone (P = 0.005). However, adjunctive SnMP did not reduce microbiological relapse rates after 5 or 6 weeks of treatment. SnMP was well tolerated and did not significantly alter gross or histological lung pathology. SnMP is a promising HDT candidate requiring further study in combination with regimens for drug-resistant TB.

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PMCID: PMC10848751
PMID: 38132181 [Indexed for MEDLINE]

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

20. The use of BPaL containing regimen in the MDR/PreXDR TB treatments in Thailand.

J Clin Tuberc Other Mycobact Dis. 2023 Dec 3;34:100408. doi: 10.1016/j.jctube.2023.100408. eCollection 2024 Feb.

Sangsayunh P(1), Sanchat T(1), Chuchottaworn C(1), Cheewakul K(2), Rattanawai S(3).

The primary objective of this study was to evaluate the real-world effectiveness, side effects and challenges associated with the implementing of the groundbreaking BPaL-containing regimen in Thailand. Another aim was to investigate the characteristics and severity of the disease, the presence of abnormal extensive lesions in chest X-Rays and the influence of cavitation on sputum conversion.
MATERIAL AND METHOD: The case series study included patients at TB clinic of Central chest institute of Thailand between August 2021-April 2023. All 28 Patients fullfilled the diagnostic criterial for MDR-TB by molecular tests and/or sputum culture. Sputum molecular test, utilizing GeneXpert MRB/XDR or Genotype MTBDRsl assay, was conducted. The 8 Pre-XDR patients who exhibited quinolone resistance and the 2 MDR-TB patients who encountered side effected from quinolone drugs were treated with BPaL regimen, while the remainder received BPaLM regimens.

RESULTS: Among the 28 patients, 23 (82.1 %) successfully completed the treatment with favorable outcomes. However, one patient from the BpaL regimen died due to severe destroy lung lesion, and four patients from the BpalM regimen discontinued treatment. The investigation into the correlation between extension lesion, cavitation lesions, and culture conversion unveiled that the group with extension lesions and cavitation ≥4 cm had a diminished probability of achieving sputum culture conversion within 8 weeks in comparison to the group without attributes. The associated risk ratio was 0.56 (95 % CI, 0.14-2.27), p = 0.14. Although the study report minimal side effects, 6 patients (22.2 %) experienced peripheral neuropathy and a notable adverse reaction identified was optic neuritis, affecting 2 cases (7.1 %).
SUMMARY: The administration of the BPaL-containing regimen resulted in rapid sputum conversion within 8 weeks and had minimal side effects.

DOI: 10.1016/j.jctube.2023.100408
PMCID: PMC10788258
PMID: 38225943

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.

21. Integrative analysis of multimodal patient data identifies personalized predictors of tuberculosis treatment prognosis.

iScience. 2024 Jan 29;27(2):109025. doi: 10.1016/j.isci.2024.109025. eCollection 2024 Feb 16.

Sambarey A(1), Smith K(1), Chung C(1), Arora HS(1), Yang Z(2), Agarwal PP(3), Chandrasekaran S(1)(4)(5).

Tuberculosis (TB) afflicted 10.6 million people in 2021, and its global burden is increasing due to multidrug-resistant TB (MDR-TB) and extensively resistant TB (XDR-TB). Here, we analyze multi-domain information from 5,060 TB patients spanning 10 countries with high burden of MDR-TB from the NIAID TB Portals database to determine predictors of TB treatment outcome. Our analysis revealed significant associations between radiological, microbiological, therapeutic, and demographic data modalities. Our machine learning model, built with 203 features across modalities outperforms models built using each modality alone in predicting treatment outcomes, with an accuracy of 83% and area under the curve of 0.84. Notably, our analysis revealed that the drug regimens Bedaquiline-Clofazimine-Cycloserine-Levofloxacin-Linezolid and

Bedaquiline-Clofazimine-Linezolid-Moxifloxacin were associated with treatment success and failure, respectively, for MDR non-XDR-TB. Drug combinations predicted to be synergistic by the INDIGO algorithm performed better than antagonistic combinations. Our prioritized set of features predictive of treatment outcomes can ultimately guide the personalized clinical management of TB.

DOI: 10.1016/j.isci.2024.109025
PMCID: PMC10865408
PMID: 38357663

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

22. Metabolites from Streptomyces aureus (VTCC43181) and Their Inhibition of Mycobacterium tuberculosis ClpC1 Protein.

Molecules. 2024 Feb 4;29(3):720. doi: 10.3390/molecules29030720.

Tran TTP(1)(2), Huynh NNT(2)(3), Pham NT(1), Nguyen DT(1), Tran CV(1), Nguyen UQ(4), Ho AN(5), Suh JW(6), Cheng J(6), Nguyen TKN(7), Tran SV(1)(2), Nguyen DM(8).

Tuberculosis is one of the most common infectious diseases in the world, caused by Mycobacterium tuberculosis. The outbreak of multiple drug-resistant tuberculosis has become a major challenge to prevent this disease worldwide. ClpC1 is a Clp ATPase protein of Mycobacterium tuberculosis, functioning as a chaperon when combined with the Clp complex. ClpC1 has emerged as a new target to discover anti-tuberculosis drugs. This study aimed to explore the ClpC1 inhibitors from actinomycetes, which have been known to provide abundant sources of antibiotics. Two cyclic peptides, including nocardamin (1), halolitoralin A (3), and a lactone pleurone (2), were isolated from the culture of Streptomyces aureus (VTCC43181). The structures of these compounds were determined based on the detailed analysis of their spectral data and comparison with references. This is the first time these compounds have been isolated from S. aureus. Compounds 1-3 were evaluated for their affection of ATPase activity of the recombinant ClpC1 protein. Of these compounds, halolitoralin A (1), a macrocyclic peptide, was effective for the ATPase hydrolysis of the ClpC1 protein.

DOI: 10.3390/molecules29030720
PMCID: PMC10856564

PMID: 38338462 [Indexed for MEDLINE]

Conflict of interest statement: The authors have declared no conflicts of interest.

23. Resistance to pyrazinamide in Mycobacterium tuberculosis complex isolates from previously treated tuberculosis cases in Southwestern Oromia, Ethiopia.

J Clin Tuberc Other Mycobact Dis. 2023 Dec 25;34:100411. doi: 10.1016/j.jctube.2023.100411. eCollection 2024 Feb.

Balay G(1), Abdella K(2), Kebede W(1)(2), Tadesse M(1)(2), Bonsa Z(1), Mekonnen M(2), Amare M(3), Abebe G(1)(2).

OBJECTIVE: Pyrazinamide (PZA) susceptibility testing is important to develop evidence-based algorithms for case management. We aimed to assess the prevalence of PZA-resistance and its impact on treatment outcomes in previously treated tuberculosis (TB) cases in southwestern Oromia, Ethiopia.
METHODS: A Phenotypic Drug Susceptibility Testing (DST) of PZA with BACTEC MGIT 960 was conducted at the Mycobacteriology Research Center of Jimma University (MRC-JU) from June to November 2021 on sixty-six Mycobacterium tuberculosis complex (MTBC) isolates from previously treated TB cases. SPSS software package version 21 was used. The differences in the proportion of PZA resistance between the groups were compared using the chi squared test. Logistic regression was used to identify the association between PZA resistance and treatment outcomes.
RESULTS: Among 66 MTBC isolates (49 rifampicin-resistant and 17 rifampicin-sensitive) included in this study, 31.8 % were resistant to PZA. The proportion of PZA resistance was almost three times higher in previously treated TB cases with rifampicin resistance than in rifampicin-sensitive patients (38.8 % vs. 11.8 %, p = 0.039). An unfavorable treatment outcome was documented for 23 % (15/65) of the participants. Patients with PZA resistance were almost four times more likely to have an unfavorable treatment outcome than patients with PZA sensitive (aOR 4.2, 95 % CI: 1.13-15.3).
CONCLUSIONS: The prevalence of PZA resistance was high compared to the pooled PZA resistance estimated worldwide. The majority of TB cases with PZA resistance had an unfavorable treatment outcome. PZA susceptibility testing should be included in the multidrug-resistant TB diagnostic algorithm to improve management of these patients.

DOI: 10.1016/j.jctube.2023.100411
PMCID: PMC10787229

PMID: 38222863

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.

Pub Med Non-Open Access

24. Linezolid-induced lactic acidosis.

BMJ Case Rep. 2024 Feb 7;17(2):e259335. doi: 10.1136/bcr-2023-259335.

Ramesh V(1), Gattu S(2), Maqsood M(3), Rao V(3).

Linezolid is a commonly prescribed antibiotic in clinical practice. Although thrombocytopenia and peripheral neuropathy are frequently encountered following prolonged administration of linezolid, lactic acidosis is a rare adverse drug reaction. We present the case of a patient on linezolid for disseminated multidrug-resistant tuberculosis who presented with vomiting, dyspnoea, hypotension and high anion gap metabolic acidosis. The initial presentation mimicked sepsis syndrome. Ketoacidosis and renal dysfunction were ruled out. There was no history of ingestion of toxins/toxic alcohols. Sepsis was unlikely because extensive radiological and microbiological testing could not identify an infection. Given the possibility of linezolid-induced lactic acidosis (LILA), linezolid was discontinued on admission. The patient's lactic acidosis resolved, and his overall condition improved. A retrospective diagnosis of LILA was thus established. LILA should be considered when patients on linezolid present with lactic acidosis and other causes for the lactic acidosis have been ruled out.

DOI: 10.1136/bcr-2023-259335
PMCID: PMC10859979
PMID: 38331448 [Indexed for MEDLINE]

Conflict of interest statement: Competing interests: None declared.

25. Differentiated service delivery framework for people with multidrug-resistant tuberculosis and HIV co-infection.

J Acquir Immune Defic Syndr. 2024 Feb 6. doi: 10.1097/QAI.0000000000003394. Online ahead of print.

Reis K(1), Wolf A(2), Perumal R(3), Seepamore B(3)(4), Guzman K(2), Ross J(2), Cheung K(5), Amico KR(6), Brust JCM(7), Padayatchi N(3), Friedland G(8), Naidoo K(3), Daftary A(3)(9), Zelnick J(10), O'Donnell M(2)(3)(11).

INTRODUCTION: For people living with HIV/AIDS, care is commonly delivered through Differentiated Service Delivery (DSD). Although people with multidrug-resistant tuberculosis (MDR-TB) and HIV/AIDS experience severe treatment associated challenges, there is no DSD model to support their treatment. In this study, we defined patterns of medication adherence and characterized longitudinal barriers to inform development of an MDR-TB/HIV DSD framework.
METHODS: Adults with MDR-TB and HIV initiating bedaquiline (BDQ) and receiving antiretroviral therapy (ART) in KwaZulu-Natal, South Africa, were enrolled and followed through the end of MDR-TB treatment. Electronic dose monitoring devices (EDM) measured BDQ and ART adherence. Longitudinal focus groups were conducted and transcripts analyzed thematically to describe discrete treatment stage-specific and cross-cutting treatment challenges.
RESULTS: 283 participants were enrolled and followed through treatment completion (median 17.8 months [IQR 16.5-20.2]). Thirteen focus groups were conducted. Most participants (82.7%, 234/283) maintained high adherence (mean BDQ adherence 95.3%; mean ART adherence 85.5%), but an adherence-challenged subpopulation with <85% cumulative adherence (17.3%, 49/283) had significant declines in mean weekly BDQ adherence from 94.9% to 39.9% ($p<0.0001$) and mean weekly ART adherence from 83.9% to 26.6% ($p<0.0001$) over 6 months. Psychosocial, behavioral, and structural obstacles identified in qualitative data were associated with adherence deficits in discrete treatment stages, and identified potential stage specific interventions.
CONCLUSION: A DSD framework for MDR-TB/HIV should intensify support for adherence-challenged subpopulations, provide multi-modal support for adherence across the treatment course and account for psychosocial, behavioral, and structural challenges linked to discrete treatment stages.

DOI: 10.1097/QAI.0000000000003394
PMID: 38323838

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

26. Genotype-Phenotype Characterization of Serial Mycobacterium tuberculosis Isolates in Bedaquiline-Resistant Tuberculosis.

Clin Infect Dis. 2024 Feb 17;78(2):269-276. doi: 10.1093/cid/ciad596.

Brown TS(1)(2), Tang L(3), Omar SV(4)(5), Joseph L(4), Meintjes G(6), Maartens G(6)(7), Wasserman S(6)(8), Shah NS(9), Farhat MR(10), Gandhi NR(9), Ismail N(4), Brust JCM(11), Mathema B(3).

BACKGROUND: Emerging resistance to bedaquiline (BDQ) threatens to undermine advances in the treatment of drug-resistant tuberculosis (DRTB). Characterizing serial Mycobacterium tuberculosis (Mtb) isolates collected during BDQ-based treatment can provide insights into the etiologies of BDQ resistance in this important group of DRTB patients.
METHODS: We measured mycobacteria growth indicator tube (MGIT)-based BDQ minimum inhibitory concentrations (MICs) of Mtb isolates collected from 195 individuals with no prior BDQ exposure who were receiving BDQ-based treatment for DRTB. We conducted whole-genome sequencing on serial Mtb isolates from all participants who had any isolate with a BDQ MIC >1 collected before or after starting treatment (95 total Mtb isolates from 24 participants).
RESULTS: Sixteen of 24 participants had BDQ-resistant TB (MGIT MIC ≥4 µg/mL) and 8 had BDQ-intermediate infections (MGIT MIC = 2 µg/mL). Participants with pre-existing resistance outnumbered those with resistance acquired during treatment, and 8 of 24 participants had polyclonal infections. BDQ resistance was observed across multiple Mtb strain types and involved a diverse catalog of mmpR5 (Rv0678) mutations, but no mutations in atpE or pepQ. Nine pairs of participants shared genetically similar isolates separated by <5 single nucleotide polymorphisms, concerning for potential transmitted BDQ resistance.
CONCLUSIONS: BDQ-resistant TB can arise via multiple, overlapping processes, including transmission of strains with pre-existing resistance. Capturing the within-host diversity of these infections could potentially improve clinical diagnosis, population-level surveillance, and molecular diagnostic test development.

DOI: 10.1093/cid/ciad596
PMID: 37874928 [Indexed for MEDLINE]

Conflict of interest statement: Potential conflicts of interest. N. S. S. reports the following grants or contracts unrelated to this work: NIH/NIAID P30AI168386 and NIH/NIAID K24AI165099. T. S. B. reports reimbursement for travel and accommodation expenses for an invited presentation for the RePORT TB International Annual Meeting 2022. G. Meintjes reports grants or contracts from the Wellcome Trust, National Institutes of Health, ImmunityBio, UK National Institute for Health and Care Research, European and Developing Countries

Clinical Trials Partnership, and South African Medical Research Council; consulting fees from Aid for AIDS; payment or honoraria for speaking or educational events from Gilead Sciences; and participation on Data Safety Monitoring or Advisory Boards for Otsuka, Drugs for Neglected Diseases Initiative, National Institutes of Health, and the Bill and Melinda Gates Medical Research Institute. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

27. Global burden of MDR-TB and XDR-TB attributable to high fasting plasma glucose from 1990 to 2019: a retrospective analysis based on the global burden of disease study 2019.

Eur J Clin Microbiol Infect Dis. 2024 Feb 17. doi: 10.1007/s10096-024-04779-x. Online ahead of print.

Chen Y(1), Liu J(1), Zhang Q(1), Chen H(1), Chai L(1), Wang Y(1), Zhang J(1), Qiu Y(1), Shen N(1), Shi X(1), Wang Q(1), Wang J(1), Li S(1), Li M(2).

PURPOSE: High fasting plasma glucose (HFPG) has been identified as a risk factor for drug-resistant tuberculosis incidence and mortality. However, the epidemic characteristics of HFPG-attributable multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) remain unclear. We aimed to analyze the global spatial patterns and temporal trends of HFPG-attributable MDR-TB and XDR-TB from 1990 to 2019.
METHODS: Utilizing data from the Global Burden of Disease 2019 project, annual deaths and disability-adjusted life years (DALYs) of HFPG-attributable MDR-TB and XDR-TB were conducted from 1990 to 2019. Joinpoint regression was employed to quantify trends over time.
RESULTS: From 1990 to 2019, the deaths and DALYs due to HFPG-attributable MDR-TB and XDR-TB globally showed an overall increasing trend, with a significant increase until 2003 to 2004, followed by a gradual decline or stability thereafter. The low sociodemographic index (SDI) region experienced the most significant increase over the past 30 years. Regionally, Sub-Saharan Africa, Central Asia and Oceania remained the highest burden. Furthermore, there was a sex and age disparity in the burden of HFPG-attributable MDR-TB and XDR-TB, with young males in the 25-34 age group experiencing higher mortality, DALYs burden and a faster increasing trend than females. Interestingly, an increasing trend followed by a stable or decreasing pattern was observed in the ASMR and ASDR of HFPG-attributable MDR-TB and XDR-TB with SDI increasing.
CONCLUSION: The burden of HFPG-attributable MDR-TB and XDR-TB rose worldwide from 1990 to 2019. These findings emphasize the importance of routine bi-directional screening and integrated management for drug-resistant TB and

diabetes.

DOI: 10.1007/s10096-024-04779-x
PMID: 38367094

28. Azetidines Kill Multidrug-Resistant Mycobacterium tuberculosis without Detectable Resistance by Blocking Mycolate Assembly.

J Med Chem. 2024 Feb 8. doi: 10.1021/acs.jmedchem.3c01643. Online ahead of print.

Cui Y(1), Lanne A(2), Peng X(3), Browne E(4), Bhatt A(2), Coltman NJ(5), Craven P(1), Cox LR(1), Cundy NJ(1), Dale K(2), Feula A(1), Frampton J(6), Fung M(7), Morton M(8), Goff A(9), Salih M(1), Lang X(3), Li X(1)(3), Moon C(10), Pascoe J(10), Portman V(4), Press C(2), Schulz-Utermoehl T(4), Lee S(7), Tortorella MD(3)(7), Tu Z(3), Underwood ZE(10), Wang C(3), Yoshizawa A(1), Zhang T(3), Waddell SJ(9), Bacon J(10), Alderwick L(2)(11), Fossey JS(1), Neagoie C(3)(7)(12).

Tuberculosis (TB) is the leading cause of global morbidity and mortality resulting from infectious disease, with over 10.6 million new cases and 1.4 million deaths in 2021. This global emergency is exacerbated by the emergence of multidrug-resistant MDR-TB and extensively drug-resistant XDR-TB; therefore, new drugs and new drug targets are urgently required. From a whole cell phenotypic screen, a series of azetidines derivatives termed BGAz, which elicit potent bactericidal activity with MIC99 values <10 μM against drug-sensitive Mycobacterium tuberculosis and MDR-TB, were identified. These compounds demonstrate no detectable drug resistance. The mode of action and target deconvolution studies suggest that these compounds inhibit mycobacterial growth by interfering with cell envelope biogenesis, specifically late-stage mycolic acid biosynthesis. Transcriptomic analysis demonstrates that the BGAz compounds tested display a mode of action distinct from the existing mycobacterial cell wall inhibitors. In addition, the compounds tested exhibit toxicological and PK/PD profiles that pave the way for their development as antitubercular chemotherapies.

DOI: 10.1021/acs.jmedchem.3c01643
PMID: 38331432

29. Unraveling Dilemmas and Lacunae in the Escalating Drug Resistance of Mycobacterium tuberculosis to Bedaquiline, Delamanid, and Pretomanid.

J Med Chem. 2024 Feb 13. doi: 10.1021/acs.jmedchem.3c01892. Online ahead of print.

Negi A(1)(2), Perveen S(1)(2), Gupta R(3)(2), Singh PP(3)(2), Sharma R(1)(2).

Delamanid, bedaquiline, and pretomanid have been recently added in the anti-tuberculosis (anti-TB) treatment regimens and have emerged as potential solutions for combating drug-resistant TB. These drugs have proven to be effective in treating drug-resistant TB when used in combination. However, concerns have been raised about the eventual loss of these drugs due to evolving resistance mechanisms and certain adverse effects such as prolonged QT period, gastrointestinal problems, hepatotoxicity, and renal disorders. This Perspective emphasizes the properties of these first-in-class drugs, including their mechanism of action, pharmacokinetics/pharmacodynamics profiles, clinical studies, adverse events, and underlying resistance mechanisms. A brief coverage of efforts toward the generation of best-in-class leads in each class is also provided. The ongoing clinical trials of new combinations of these drugs are discussed, thus providing a better insight into the use of these drugs while designing an effective treatment regimen for resistant TB cases.

DOI: 10.1021/acs.jmedchem.3c01892
PMID: 38351709

30. Pharmacokinetics and Optimal Dosing of Levofloxacin in Children for Drug-Resistant Tuberculosis: An Individual Patient Data Meta-Analysis.

Clin Infect Dis. 2024 Feb 10:ciae024. doi: 10.1093/cid/ciae024. Online ahead of print.

White YN(1), Solans BP(1)(2), Denti P(3), van der Laan LE(3)(4), Schaaf HS(4), Vonasek B(5), Malik AA(6)(7), Draper HR(4), Hussain H(6), Hesseling AC(4), Garcia-Prats AJ(4)(5), Savic RM(1)(2).

BACKGROUND: Each year 25 000-32 000 children develop rifampicin- or multidrug-resistant tuberculosis (RR/MDR-TB), and many more require preventive treatment. Levofloxacin is a key component of RR/MDR-TB treatment and prevention, but the existing pharmacokinetic data in children have not yet been comprehensively summarized. We aimed to characterize levofloxacin pharmacokinetics through an individual patient data meta-analysis of available studies and to determine optimal dosing in children.
METHODS: Levofloxacin concentration and demographic data were pooled from 5 studies and analyzed using nonlinear mixed effects modeling. Simulations were performed using current World Health Organization (WHO)-recommended and

model-informed optimized doses. Optimal levofloxacin doses were identified to target median adult area under the time-concentration curve (AUC)24 of 101 mg·h/L given current standard adult doses.
RESULTS: Data from 242 children (2.8 years [0.2-16.8] was used). Apparent clearance was 3.16 L/h for a 13-kg child. Age affected clearance, reaching 50% maturation at birth and 90% maturation at 8 months. Nondispersible tablets had 29% lower apparent oral bioavailability compared to dispersible tablets. Median exposures at current WHO-recommended doses were below the AUC target for children weighing <24 kg and under <10 years, resulting in approximately half of the exposure in adults. Model-informed doses of 16-33 mg/kg for dispersible tablets or 16-50 mg/kg for nondispersible tablets were required to meet the AUC target without significantly exceeding the median adult Cmax.
CONCLUSIONS: Revised weight-band dosing guidelines with doses of >20 mg/kg are required to ensure adequate exposure. Further studies are needed to determine safety and tolerability of these higher doses.

DOI: 10.1093/cid/ciae024
PMID: 38340060

Conflict of interest statement: Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

31. Design and synthesis of benzo[b]thiophene-based hybrids as novel antitubercular agents against MDR/XDR Mycobacterium tuberculosis.

Arch Pharm (Weinheim). 2024 Feb;357(2):e2300529. doi: 10.1002/ardp.202300529. Epub 2023 Nov 9.

Al-Warhi T(1), Rashad NM(2), Almahli H(3), Abdel-Aziz MM(4), Elsayed ZM(2), Shahin MI(5), Eldehna WM(6).

In an effort to support the global fight against tuberculosis (TB), which is widely recognized as the most lethal infectious disease worldwide, we present the design and synthesis of new benzo[b]thiophene-based hybrids as promising candidates for the management of multidrug-resistant (MDR)/extensively drug-resistant (XDR) Mycobacterium tuberculosis. The isatin motif was incorporated into the target hybrids as it represents a privileged scaffold in antitubercular drug discovery. Since lipophilicity plays a pivotal role in the anti-TB agents' activity, the lipophilicity of the target hybrids was manipulated via the development of two series of N-1 methyl and N-1 benzyl

substituted isatins (6a-h and 9a-h, respectively). Screening of the target hybrids was first performed against drug-sensitive M. tuberculosis (ATCC 25177). The structure-activity relationship outputs highlighted that incorporation of 3-unsubstituted benzo[b]thiophene and 5-methoxy isatin moieties was favorable for the antimycobacterial activity. Thereafter, the most potent molecules (6b-h, 9c-e, and 9h) were evaluated against the resistant strains MDR-TB (ATCC 35822) as well as against XDR-TB (RCMB 2674) where they displayed promising activity. To evaluate the safety of the target hybrids, an sulforhodamine B assay was conducted to determine their possible cytotoxic effects on VERO cells.

DOI: 10.1002/ardp.202300529
PMID: 37946574 [Indexed for MEDLINE]

32. Model-based dose optimization framework for bedaquiline, pretomanid and linezolid for the treatment of drug-resistant tuberculosis.

Br J Clin Pharmacol. 2024 Feb;90(2):463-474. doi: 10.1111/bcp.15925. Epub 2023 Oct 26.

Mehta K(1), Guo T(1), van der Graaf PH(1)(2), van Hasselt JGC(1).

AIMS: Bedaquiline, pretomanid and linezolid (BPaL) combination treatment against Mycobacterium tuberculosis is promising, yet safety and adherence concerns exist that motivate exploration of alternative dosing regimens. We developed a mechanistic modelling framework to compare the efficacy of the current and alternative BPaL treatment strategies.
METHODS: Pharmacodynamic models for each drug in the BPaL combination treatment were developed using in vitro time-kill data. These models were combined with pharmacokinetic models, incorporating body weight, lesion volume, site-of-action distribution, bacterial susceptibility and pharmacodynamic interactions to assemble the framework. The model was qualified by comparing the simulations against the observed clinical data. Simulations were performed evaluating bedaquiline and linezolid approved (bedaquiline 400 mg once daily [QD] for 14 days followed by 200 mg three times a week, linezolid 1200 mg QD) and alternative dosing regimens (bedaquiline 200 mg QD, linezolid 600 mg QD).
RESULTS: The framework adequately described the observed antibacterial activity data in patients following monotherapy for each drug and approved BPaL dosing. The simulations suggested a minor difference in median time to colony forming unit (CFU)-clearance state with the bedaquiline alternative compared to the approved dosing and the linezolid alternative compared to the approved dosing. Median time to non-replicating-clearance state was predicted to be 15 days from the CFU-clearance state.

CONCLUSIONS: The model-based simulations suggested that comparable efficacy can be achieved using alternative bedaquiline and linezolid dosing, which may improve safety and adherence in drug-resistant tuberculosis patients. The framework can be utilized to evaluate treatment optimization approaches, including dosing regimen and duration of treatment predictions to eradicate both replicating- and non-replicating bacteria from lung and lesions.

DOI: 10.1111/bcp.15925
PMID: 37817504 [Indexed for MEDLINE]

33. Compliance with new drug use and the effect of discrepant drug susceptibility testing on MDR/RR-TB treatment.

Int J Tuberc Lung Dis. 2024 Feb 1;28(2):18-24. doi: 10.5588/ijtld.23.0237.

Shin JE(1), Jeon D(2), Mok J(3), Yim JJ(4), Kwon YS(5), Jo KW(1), Shim TS(1).

BACKGROUND: Following the WHO???s announcement in 2018, the use of new drugs was recommended for all patients with multidrug-resistant TB (MDR-TB) in Korea. This study aimed to evaluate adherence to new anti-TB drug regimens and implementation of molecular drug susceptibility testing (mDST) in Korea.METHODS: Nationwide, 560 patients were reported as having MDR-TB in 2021. The implementation of mDST and new anti-TB drug use were analysed. The discrepancy between mDST and phenotypic DST (pDST) results and their implications on the use of new anti-TB drugs were also analysed. The use of novel anti-TB drugs has been approved by the National TB Expert Committee.RESULTS: The non-adherence rate in MDR-TB patients was 14.3%. The mDST implementation rate was 96.1%. Of the 459 patients who underwent both mDST and pDST, the discordance rate for rifampicin (RIF) resistance was 22.6% (n = 104), of which 72.1% (n = 75) were resistant on mDST but susceptible on pDST. The discrepancy in mDST and pDST results related to RIF resistance was found to be the main cause of non-adherence to new drug regimen.CONCLUSION: Comprehensive training on how to interpret conflicting results between mDST and pDST could enhance the utilisation of new drugs in the treatment of MDR/RIF-resistant TB.

DOI: 10.5588/ijtld.23.0237
PMID: 38303037 [Indexed for MEDLINE]

34. Bedaquiline, pretomanid, and linezolid with or without moxifloxacin for tuberculosis.

Lancet Respir Med. 2024 Feb;12(2):e5-e6. doi: 10.1016/S2213-2600(23)00426-5. Epub 2023 Nov 30.

Labuda SM(1), Seaworth B(2), Dasgupta S(3), Goswami ND(4); BPaL Accelerated Monitoring Project Team.

DOI: 10.1016/S2213-2600(23)00426-5
PMID: 38043563 [Indexed for MEDLINE]

35. Co-resistance to isoniazid and second-line anti-tuberculosis drugs in isoniazid-resistant tuberculosis at a tertiary care hospital in Thailand.

Microbiol Spectr. 2024 Feb 7:e0346223. doi: 10.1128/spectrum.03462-23. Online ahead of print.

Prommi A(1)(2), Wongjarit K(3)(4), Petsong S(3), Somsukpiroh U(5), Faksri K(6)(7), Kawkitinarong K(8)(9), Payungporn S(2)(10), Rotcheewaphan S(2)(3).

Isoniazid-resistant tuberculosis (Hr-TB) is an important drug-resistant tuberculosis (TB). In addition to rifampicin, resistance to other medications for Hr-TB can impact the course of treatment; however, there are currently limited data in the literature. In this study, the drug susceptibility profiles of Hr-TB treatment and resistance-conferring mutations were investigated for Hr-TB clinical isolates from Thailand. Phenotypic drug susceptibility testing (pDST) and genotypic drug susceptibility testing (gDST) were retrospectively and prospectively investigated using the Mycobacterium Growth Indicator Tube (MGIT), the broth microdilution (BMD) method, and whole-genome sequencing (WGS)-based gDST. The prevalence of Hr-TB cases was 11.2% among patients with TB. Most Hr-TB cases (89.5%) were newly diagnosed patients with TB. In the pDST analysis, approximately 55.6% (60/108) of the tested Hr-TB clinical isolates exhibited high-level isoniazid resistance. In addition, the Hr-TB clinical isolates presented co-resistance to ethambutol (3/161, 1.9%), levofloxacin (2/96, 2.1%), and pyrazinamide (24/118, 20.3%). In 56 Hr-TB clinical isolates, WGS-based gDST predicted resistance to isoniazid [katG S315T (48.2%) and fabG1 c-15t (26.8%)], rifampicin [rpoB L430P and rpoB L452P (5.4%)], and fluoroquinolones [gyrA D94G (1.8%)], but no mutation for ethambutol was detected. The categorical agreement for the detection of resistance to isoniazid, rifampicin, ethambutol, and levofloxacin between WGS-based gDST and the MGIT or the BMD method ranged from 80.4% to 98.2% or 82.1% to 100%, respectively. pDST and gDST demonstrated a low co-resistance rate between isoniazid and second-line TB drugs in Hr-TB clinical isolates.IMPORTANCEThe prevalence of isoniazid-resistant tuberculosis (Hr-TB) is the highest among other types of drug-resistant tuberculosis. Currently, the World Health Organization (WHO) guidelines recommend the treatment of Hr-TB with rifampicin, ethambutol, pyrazinamide, and levofloxacin for 6 months. The

susceptibility profiles of Hr-TB clinical isolates, especially when they are co-resistant to second-line drugs, are critical in the selection of the appropriate treatment regimen to prevent treatment failure. This study highlights the susceptibility profiles of the WHO-recommended treatment regimen in Hr-TB clinical isolates from a tertiary care hospital in Thailand and the concordance and importance of using the phenotypic drug susceptibility testing or genotypic drug susceptibility testing for accurate and comprehensive interpretation of results.

DOI: 10.1128/spectrum.03462-23
PMID: 38323824

36. Role of the IL8 rs4073 polymorphism in central nervous system toxicity in patients receiving multidrug-resistant tuberculosis treatment.

J Bras Pneumol. 2024 Feb 12;50(1):e20230338. doi: 10.36416/1806-3756/e20230338. eCollection 2024.

[Article in English, Portuguese]

Badamasi IM(1), Muhammad M(1), Umar AA(1), Madugu UM(1), Gadanya MA(2), Aliyu IA(3), Kabir IM(3), Umar IA(4), Johnson O(5), Stanslas J(6).

OBJECTIVE: To determine the role of the IL8 rs4073 polymorphism in predicting the risk of central nervous system (CNS) toxicity in patients receiving standard pharmacological treatment for multidrug-resistant tuberculosis (MDR-TB).
METHODS: A cohort of 85 consenting MDR-TB patients receiving treatment with second-line antituberculosis drugs had their blood samples amplified for the IL8 (rs4073) gene and genotyped. All patients were clinically screened for evidence of treatment toxicity and categorized accordingly. Crude and adjusted associations were assessed.
RESULTS: The chief complaints fell into the following categories: CNS toxicity; gastrointestinal toxicity; skin toxicity; and eye and ear toxicities. Symptoms of gastrointestinal toxicity were reported by 59% of the patients, and symptoms of CNS toxicity were reported by 42.7%. With regard to the genotypes of IL8 (rs4073), the following were identified: AA, in 64 of the study participants; AT, in 7; and TT, in 11. A significant association was found between the dominant model of inheritance and CNS toxicity for the crude model (p = 0.024; OR = 3.57; 95% CI, 1.18-10.76) and the adjusted model (p = 0.031; OR = 3.92; 95% CI, 1.13-13.58). The AT+TT genotype of IL8 (rs4073) showed a 3.92 times increased risk of CNS toxicity when compared with the AA genotype.
CONCLUSIONS: The AT+TT genotype has a tendency to be associated with an increased risk of adverse clinical features during MDR-TB treatment.

DOI: 10.36416/1806-3756/e20230338
PMID: 38359298 [Indexed for MEDLINE]

37. Unsuccessful tuberculosis treatment outcomes across Brazil's geographical landscape before and during the COVID-19 pandemic: are we truly advancing toward the sustainable development/end TB goal?

Infect Dis Poverty. 2024 Feb 18;13(1):17. doi: 10.1186/s40249-024-01184-6.

Tavares RBV(1), Berra TZ(2), Alves YM(2), Popolin MAP(3), Ramos ACV(4), Tártaro AF(2), de Souza CF(2), Arcêncio RA(2).

BACKGROUND: Tuberculosis is one of the most significant infectious diseases for global public health. The reallocation of healthcare resources and the restrictions imposed by the COVID-19 pandemic have hindered access to TB diagnosis and treatment. Increases in unfavorable outcomes of the disease have been observed in Brazil. The objective of this study was to analyze the spatial distribution of unfavorable TB treatment outcomes in Brazil before and during the pandemic.
METHODS: An ecological study with spatial analysis was conducted with all 5569 municipalities in Brazil. All reported cases of tuberculosis between January 2010 and December 2021, as well as reported cases of COVID-19 from February 2020 to December 2021, were included. The outcomes studied encompass loss to follow-up, drug-resistant tuberculosis, and death. The Getis Ord GI* technique was employed to assess spatial association, and the Kernel density estimator was used to identify areas with concentrated increases or decreases in outcomes. Bivariate Local Moran's I was used to examine the spatial association between outcomes and COVID-19 incidence. The study was approved by the Research Ethics Committee of Ribeirão Preto Nursing School, University of São Paulo.
RESULTS: There were 134,394 cases of loss to follow-up, 10,270 cases of drug resistance, and 37,863 deaths. Clusters of high and low values were identified for all three outcomes, indicating significant changes in the spatial distribution patterns. Increases in concentrations were observed for lost to follow-up cases in the Southeast, while reductions occurred in the Northeast, South, and Midwest. Drug-resistant tuberculosis experienced an increase in the Southern and Southeastern regions and a decrease in the Northeast and South. TB-related deaths showed notable concentrations in the Midwest, Northeast, South, and Southeast. There was an increase in high occurrence clusters for deaths after 2020 and 2021 in the Northeast.
CONCLUSIONS: The pandemic has brought additional challenges, emphasizing the importance of enhancing efforts and disease control strategies, prioritizing early identification, treatment adherence, and follow-up. This commitment is vital for achieving the goal of tuberculosis elimination.

DOI: 10.1186/s40249-024-01184-6
PMCID: PMC10874548
PMID: 38369536 [Indexed for MEDLINE]

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

38. Novel indolinone-tethered benzothiophenes as anti-tubercular agents against MDR/XDR M. tuberculosis: Design, synthesis, biological evaluation and in vivo pharmacokinetic study.

Bioorg Chem. 2024 Feb;143:107009. doi: 10.1016/j.bioorg.2023.107009. Epub 2023 Nov 29.

Eldehna WM(1), Mahmoud ST(2), Elshnawey ER(3), Elsayed ZM(3), Majrashi TA(4), El-Ashrey MK(5), Rashed M(6), Hemeda LR(7), Shoun AA(8), Elkaeed EB(9), El Hassab MA(10), Abdel-Aziz MM(11), Shahin MI(12).

Joining the global effort to eradicate tuberculosis, one of the deadliest infectious killers in the world, we disclose in this paper the design and synthesis of new indolinone-tethered benzothiophene hybrids 6a-i and 7a-i as potential anti-tubercular agents. The MICs were determined in vitro for the synthesized compounds against the sensitive M. tuberculosis strain ATCC 25177. Potent compounds 6b, 6d, 6f, 6h, 7a, 7b, 7d, 7f, 7h and 7i were furtherly assessed versus resistant MDR-TB and XDR-TB. Structure activity relationship investigation of the synthesized compounds was illustrated, accordingly. Superlative potency was unveiled for compound 6h (MIC = 0.48, 1.95 and 7.81 µg/mL for ATCC 25177 sensitive TB strain, resistant MDR-TB and XDR-TB, respectively). Moreover, validated in vivo pharmacokinetic study was performed for the most potent derivative 6h revealing superior pharmacokinetic profile over the reference drug. For further exploration of the anti-tubercular mechanism of action, molecular docking was carried out for the former compound in DprE1 active site as one of the important biological targets of TB. The binding mode and the docking score uncovered exceptional binding when compared to the co-crystallized ligand suggesting that it maybe the underlying target for its outstanding anti-tubercular potency.

DOI: 10.1016/j.bioorg.2023.107009
PMID: 38070474 [Indexed for MEDLINE]

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.

39. Pediatric Multidrug-Resistant Disseminated Tuberculosis Presenting as Small Finger Tuberculous Osteomyelitis: A Case Report.

JBJS Case Connect. 2024 Feb 2;14(1). doi: 10.2106/JBJS.CC.23.00445. eCollection 2024 Jan 1.

Hoffman CJ(1), France T(1), Cram T(1), Bodmer JL(2), Sanders JS(1)(3).

CASE: We report a case in the United States of a 12-year-old girl with multidrug-resistant tuberculous (MDR-TB) osteomyelitis of the hand managed with surgical debridement and second-line anti-TB therapy. The disease course was complicated by dissemination and multifocal progression.
CONCLUSION: Despite early intervention, multidrug resistance makes TB treatment challenging and facilitated progression to disseminated disease in this case. We review the difficulties in diagnosis and treatment of pediatric MDR-TB.

DOI: 10.2106/JBJS.CC.23.00445
PMID: 38306445 [Indexed for MEDLINE]

Conflict of interest statement: Disclosure: The Disclosure of Potential Conflicts of Interest forms are provided with the online version of the article (http://links.lww.com/JBJSCC/C294).

40. Comparison of the MeltPro TB assay and whole-genome sequencing assay for rapid molecular diagnosis of drug resistant tuberculosis in guangdong province.

Diagn Microbiol Infect Dis. 2024 Feb;108(2):116128. doi: 10.1016/j.diagmicrobio.2023.116128. Epub 2023 Nov 2.

Yu M(1), Zhang C(1), Xu L(1), Peng K(1), Qiu H(2), Zhuo W(1), Zhao Y(1), Wu Z(1), Chen X(1), Chen Y(1), Liao Q(1), Huang Y(2), Wei W(3).

BACKGROUND: Rifampicin (RIF) and multidrug-resistant tuberculosis (TB) are major public health threats. As conventional phenotypic drug susceptibility testing requires two-eight weeks, molecular diagnostic assays are widely used to determine drug resistance.
METHODS: Clinical Mycobacterium tuberculosis isolates with consistent drug

susceptibility results, tested using microbroth dilution and proportion methods in Löwenstein-Jensen medium from patients with TB in Guangdong province were utilized to evaluate MeltPro TB and whole-genome sequencing (WGS) assays in detecting resistance to RIF, isoniazid (INH), ethambutol (EMB), fluoroquinolones (FQ), and streptomycin (SM). Solid phenotypic drug susceptibility testing was used as the gold standard to evaluate the detection capacity of MeltPro TB on clinical sputum samples of patients with TB.
RESULTS: Similar to WGS, MeltPro TB successfully detected RIF, INH, and SM resistance with sensitivities of 86.3, 84.8, and 86.6 %, respectively. However, the resistant isolate detection rates were only 58.1 and 69.6 % for EMB and FQ-resistant strains. For clinical specimens, MeltPro TB still showed good detectable rates of RIF and INH resistance, with sensitivities of 82.4 % and 95.2 %, respectively. Detectable rates of FQ and EMB resistance were low: 77.8 % and 35.3 %, respectively.
CONCLUSIONS: MeltPro TB can detect known DNA mutations associated with drug resistance in Mycobacterium tuberculosis strains with comparable efficacy to WGS. For FQ and EMB resistance testing, MeltPro TB requires optimization and is unsuitable for general use. MeltPro TB can be used for diagnosis of RIF and multidrug-resistant tuberculosis to rapidly initiate appropriate anti-TB drug therapy.

DOI: 10.1016/j.diagmicrobio.2023.116128
PMID: 38007912 [Indexed for MEDLINE]

Conflict of interest statement: Declaration of Competing Interest We have declared that there were no competing interests.

41. Diagnosing osteoarticular tuberculosis and detecting rifampicin resistance: A comparative analysis of Truenat MTB Plus vs GeneXpert Ultra.

Tuberculosis (Edinb). 2024 Mar;145:102483. doi: 10.1016/j.tube.2024.102483. Epub 2024 Feb 1.

Sharma K(1), Sharma M(2), Sharma A(3), Dhillon MS(4).

SETTING: Diagnosing osteoarticular tuberculosis (OATB) and detecting drug resistance is a challenge in an endemic country like India.
OBJECTIVE: Truenat MTB Plus assay (TruPlus), a chip-based portable machine, was compared with GeneXpert Ultra (GxUltra) for diagnosing drug-resistant OATB.
DESIGN: 115 synovial fluid and pus specimens [22 culture-positive confirmed, 58 culture-negative clinically-suspected, 35 non-TB controls] processed between 2017 and 2023 were subjected to TruPlus, GxUltra and multiplex-PCR for

diagnosing OATB. They were further screened for rifampicin resistance using TruRif chip. The performance was evaluated against composite reference standard, phenotypic drug susceptibility testing and rpoB gene sequencing.
RESULTS: TruPlus, GxUltra and MPCR detected 77.5 %, 71.25 %, and 83.75 %, cases of OATB, respectively. TruPlus detected five additional cases missed by GxUltra. The performance of TruPlus was comparable to GxUltra (p = 0.074) and to MPCR (p = 0.074), while performance of GxUltra was significantly inferior to MPCR (p = 0.004). The overall agreement with reference standard was substantial for TruPlus and MPCR and moderate for GxUltra. Both TruRif and GxUltra reported 4 cases as rifampicin resistant.
CONCLUSION: TruPlus along with TruRif offers better sensitivity than GxUltra. Its compact and portable platform allows wider application in peripheral settings, thus making it a pragmatic solution for diagnosing OATB and its drug resistance.

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42. Whole genome sequencing for the prediction of resistant tuberculosis strains from northern India.

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PURPOSE: Tuberculosis is an important public health problem among infectious diseases. The problem becomes more concerning with the emergence of MDR-TB and pre-XDR-TB. Whole genome sequencing (WGS) detection of resistance has recently gained popularity as it has advantages over other commercial techniques.
METHODS: We performed in-house WGS followed by detailed analysis by an in-house pipeline to identify the resistance markers. This was accompanied by Phenotypic DST, and Sanger sequencing on all the 12 XDR, 06 pre-XDR, and 06 susceptible M. tb isolates. These results were collated with online M. tb WGS pipelines (TB profiler, PhyResSE, Mykrobe predictor) for comparative analysis.
RESULTS: Following our in-house analysis, we observed 64 non-synonymous SNPs, fifteen synonymous SNPs, and five INDELs in 25 drug resistance-associated genes/intergenic regions (IGRs) in M. tb isolates. Sensitivity for detecting XDR

is 33%, 58%, 83%, and 83%, respectively, using Mykrobe predictor, PhyResSE, TB-profiler, and in-house pipeline for WGS analysis, respectively. TB-profiler detected a rare mutation H70R in the gyrA gene in one pre-XDR isolate. Lineage 2.2.1 East-Asian (Beijing sublineage type) predominated (60%) in WGS data analysis of the XDR isolates.
CONCLUSIONS: Our findings suggest that in-house analysis of WGS data and TB-profiler sensitivity was better for the detection of second-line resistance as compared to other automated tested tools. Frequent upgradation of newer mutations associated with resistance needs to be updated, as it potentiates tailored treatment for patients.

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43. High frequency of isoniazid and fluroquinolone resistance among patients with rifampicin sensitive tuberculosis.

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Jain P(1), Ratnam R(1), Sengupta S(1), Singh U(1), Kumar V(1), Jain A(2).

This study was done to determine frequency of isoniazid (INH) and fluoroquinolones FQ resistance among rifampicin sensitive strains of Mycobacterium tuberculosis and to study their mutation patterns. Retrospective analysis was done for samples with M. tuberculosis detected by Cartridge based NAAT (CBNAAT). They were tested sequentially by first line (FL) and second line - line probe assay (SL-LPA) depending on their drug resistance pattern and following diagnostic algorithm. Total 9722 (74.1 %) of 13124 NAAT positive samples were sensitive for rifampicin. On FL-LPA, 833 (8.6 %) were resistant to INH and of which 110 (13.2 %) were also resistant to FQ by SL-LPA. Most common mutations observed for INH resistance were katG S315T1 mutation in 615 (97.3 %) strains, inhA C15T mutation in 174 (86.6 %) strains and for FQ resistance were gyrA D94G mutation in 46 (41.8 %) strains. Heteroresistance, inferred mutations, combination of mutations and unique mutations were also observed in all genes.

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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.

44. Insidious transmission of Mycobacterium tuberculosis in Ordos, China: a molecular epidemiology study.

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BACKGROUND: In this study, we conducted this population-based study to evaluate the genetic diversity and clustering rate of Mycobacterium tuberculosis (MTB) strains using the whole-genome sequencing (WGS), to better understand its transmission in Ordos.
METHODS: All patients with culture-positive TB notified in Ordos from January 2021 to December 2022 were recruited. WGS was performed to analyze single-nucleotide polymorphism (SNP) and to identify genotypic drug susceptibilities of MTB isolates.
RESULTS: Overall, a total of 186 patients were included in the present study, of whom 35 (18.8%) had no symptoms suggestive of active TB. Lineage 2 was the predominant MTB sublineage, accounting for 186 of isolates tested. When the pairwise SNP difference ≤ 12 was used as the cutoff for WGS-based clusters, we identified 17 genotypic clusters, and 38 isolates belonged to these 17 clusters, resulting in a clustering rate of 20.4%. The Beijing genotype was an independent factor associating with genomic-clustering (adjusted OR 4.219, 95% CI 0.962-18.502). The overall sensitivity on WGS-based resistance prediction was 85.7% for rifampicin, 73.1% for isoniazid, 60.0% for Ethambutol, 72.7% for streptomycin, and 72.7% for fluoroquinolones.
CONCLUSION: To conclude, the present study demonstrates the extensive recent transmission of Beijing genotype strains in the community of Ordos. The failure to provide a comprehensive pattern of transmission indicated the missed diagnosis of active TB within the community. A substantial proportion of subclinical TB cases are recognized in the bacteria-positive cases, emphasizing that we must interrupt transmission by finding people with active TB before they infect others.

DOI: 10.1007/s10096-023-04730-6
PMID: 38055064 [Indexed for MEDLINE]

45. Computational insights into potential marine natural products as selective inhibitors of Mycobacterium tuberculosis InhA: A structure-based virtual screening study.

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Several factors are associated with the emergence of drug resistance mechanisms, such as impermeable cell walls, gene mutations, and drug efflux systems. Consequently, bacteria acquire resistance, leading to a decrease in drug efficacy. A new and innovative strategy is required to combat drug resistance in tuberculosis (TB) effectively. Therefore, targeting the mycolic acid biosynthesis pathway, which is involved in synthesising mycolic acids (MAs), essential structural components responsible for mycobacterial pathogenicity, has garnered interest in TB research and the concept of drug resistance. In this context, InhA, which plays a crucial role in the fatty acid synthase-II (FAS-II) system of the MA biosynthetic pathway, was selected as a druggable target for screening investigation. To identify potential lead molecules against InhA, diverse marine natural products (MNPs) were collected from the comprehensive marine natural products database (CMNPD). Virtual screening studies aided in selecting potential lead molecules that best fit within the substrate-binding pocket (SBP) of InhA, forming crucial hydrogen bond interaction with the catalytic residue Tyr158. Three MNPs, CMNPD30814, CMNPD1702, and CMNPD27355, were chosen as prospective alternative molecules due to their favorable pharmacokinetic properties and lack of toxicity according to ProTox-II predictions. Additionally, improved reactivity of the MNPs was observed in the results of density functional theory (DFT) studies. Furthermore, comparative molecular dynamics simulation (MDS), principal component (PC)-based free energy landscape (FEL) analysis, and molecular mechanics Poisson-Boltzmann surface area (MM-PBSA) were employed to show enhanced structural stability, increased H-bond potential, and high binding affinity toward the target InhA. Moreover, the hot spot residues that contributed to the high binding energy profile and anchored the stability of the complexes were revealed with their individual interaction energy. The computational insights from this study provide potential avenues to

combat TB through the multifaceted mode of action of these marine lead molecules, which can be further explored in future experimental investigations.

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