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1. Epidemiology of extensively drug-resistant tuberculosis among patients with multidrug-resistant tuberculosis: A systematic review and meta-analysis.

Int J Infect Dis. 2023 Jul;132:50-63. doi: 10.1016/j.ijid.2023.04.392. Epub 2023 Apr 16.

Diriba G(1), Alemu A(2), Yenew B(2), Tola HH(3), Gamtesa DF(2), Mollalign H(2), Eshetu K(4), Moga S(2), Abdella S(2), Tollera G(2), Kebede A(5), Dangisso MH(2).

OBJECTIVES: To estimate the pooled proportion of extensively drug-resistant tuberculosis (XDR-TB) and pre-extensively drug-resistant tuberculosis (pre-XDR-TB) in patients with multidrug-resistant TB (MDR-TB).
METHODS: We systematically searched articles from electronic databases: MEDLINE (PubMed), ScienceDirect, and Google Scholar. We also searched gray literature from the different literature sources main outcome of the review was either XDR-TB or pre-XDR-TB in patients with MDR-TB. We used the random-effects model, considering the substantial heterogeneity among studies. Heterogeneity was assessed by subgroup analyses. STATA version 14 was used for analysis.
RESULTS: A total of 64 studies that reported on 12,711 patients with MDR-TB from 22 countries were retrieved. The pooled proportion of pre-XDR-TB was 26% (95% confidence interval [CI]: 22-31%), whereas XDR-TB in MDR-TB cases was 9% (95% CI: 7-11%) in patients treated for MDR-TB. The pooled proportion of resistance to fluoroquinolones was 27% (95% CI: 22-33%) and second-line injectable drugs was 11% (95% CI: 9-13%). Whereas the pooled resistance proportions to bedaquiline, clofazimine, delamanid, and linezolid were 5% (95% CI: 1-8%), 4% (95% CI: 0-10%), 5% (95% CI; 2-8%), and 4% (95% CI: 2-10%), respectively.
CONCLUSION: The burden of pre-XDR-TB and XDR-TB in MDR-TB were considerable. The high burdens of pre-XDR-TB and XDR-TB in patients treated for MDR-TB suggests the need to strengthen TB programs and drug resistance surveillance.

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PMCID: PMC10302157
PMID: 37072053 [Indexed for MEDLINE]

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

2. Continuous surveillance of drug-resistant TB burden in Rwanda: a retrospective cross-sectional study.

Int Health. 2023 Jul 4;15(4):357-364. doi: 10.1093/inthealth/ihac039.

Habimana-Mucyo Y(1), Dushime A(1), Migambi P(1), Habiyambere I(1), Semuto Ngabonziza JC(2)(3), Decroo T(4).

BACKGROUND: Since the roll-out of the Xpert MTB/RIF assay, continuous surveillance can provide an estimate of rifampicin-resistant TB (RR-TB) prevalence, provided high drug susceptibility testing (DST) coverage is achieved. We use national data from Rwanda to describe rifampicin DST coverage, estimate the prevalence of RR-TB and assess its predictors.
METHODS: Routinely collected DST data were entered into an electronic TB case-based surveillance system. DST coverage was calculated among all bacteriologically confirmed pulmonary TB patients notified from 1 July 2019 to 30 June 2020 in Rwanda. The prevalence of RR-TB was estimated among those with DST results. Univariable and multivariable analysis was performed to explore predictors for RR TB.
RESULTS: Among 4066 patients with bacteriologically confirmed pulmonary TB, rifampicin DST coverage was 95.6% (4066/4251). RR-TB was diagnosed in 73 patients. The prevalence of RR-TB was 1.4% (53/3659; 95% CI 1.09 to 1.89%) and 4.9% (20/406; 95% CI 3.03 to 7.51%) in new and previously treated TB cases, respectively. Predictors of RR-TB were: (1) living in Kigali City (adjusted OR [aOR] 1.65, 95% CI 1.03 to 2.65); (2) previous TB treatment (aOR 3.64, 95% CI 2.14 to 6.19); and (3) close contact with a known RR-TB patient (aOR 11.37, 95% CI 4.19 to 30.82).
CONCLUSIONS: High rifampicin DST coverage for routine reporting allowed Rwanda to estimate the RR-TB prevalence among new and previously treated patients.

DOI: 10.1093/inthealth/ihac039
PMCID: PMC10318964
PMID: 35653710 [Indexed for MEDLINE]

Conflict of interest statement: None declared.

3. Bedquiline Resistance Mutations: Correlations with Drug Exposures and Impact on the Proteome in M. tuberculosis.

Antimicrob Agents Chemother. 2023 Jul 18;67(7):e0153222. doi: 10.1128/aac.01532-22. Epub 2023 May 31.

Xu J(1), Li D(1), Shi J(1), Wang B(1), Ge F(1), Guo Z(1), Mu X(1), Nuermberger

E(2)(3), Lu Y(1).

Bedaquiline (BDQ) is an effective drug for the treatment of drug-resistant tuberculosis. Mutations in atpE, which encodes the target of BDQ, are associated with large increases in MICs. Mutations in Rv0678 that derepress the transcription of the MmpL5-MmpS5 efflux transporter are associated with smaller increases in MICs. However, Rv0678 mutations are the most common mutations that are associated with BDQ resistance in clinical isolates, and they also confer cross-resistance to clofazimine (CFZ). To investigate the mechanism of BDQ resistance and the correlation between Rv0678 mutations and target-based atpE mutations, M. tuberculosis strains were exposed to different concentrations of BDQ or CFZ to select Rv0678 mutations and atpE mutations. Gene overexpression strains were constructed to illustrate the roles of MmpL5 and MmpS5. A quantitative proteome analysis was performed to compare the BDQ-resistant mutants to the isogenic strain H37Rv. Here, we report that the Rv0678 mutations were more readily selected than were the atpE mutations at low concentrations of BDQ or CFZ. The atpE mutations were selected by high concentrations of BDQ exposure. The overexpression of both mmpL5 and mmpS5 reduced the susceptibility of Mycobacterium tuberculosis to BDQ and CFZ. Secreted immunogenic proteins and proteins involved in the biosynthesis and transport of phthiocerol dimycocerosates were associated with Rv0678 mutations conferring BDQ resistance in the proteome analysis. In conclusion, exposure to different bedaquiline concentrations resulted in the selection of different mutations. The coexpression of MmpL5 and MmpS5 contributed to drug resistance and upregulated pathogenic proteins in M. tuberculosis, suggesting MmpL5-MmpS5 as a new potential target for antituberculosis drug development. These results warrant further surveillance for the evolution of BDQ resistance during clinical usage.

DOI: 10.1128/aac.01532-22
PMCID: PMC10353445
PMID: 37255473 [Indexed for MEDLINE]

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

4. QT Interval Prolongation with One or More QT-Prolonging Agents Used as Part of a Multidrug Regimen for Rifampicin-Resistant Tuberculosis Treatment: Findings from Two Pediatric Studies.

Antimicrob Agents Chemother. 2023 Jul 18;67(7):e0144822. doi: 10.1128/aac.01448-22. Epub 2023 Jun 26.

Ali AM(1)(2), Radtke KK(1), Hesseling AC(3), Winckler J(3), Schaaf HS(3), Draper HR(3), Solans BP(1), van der Laan L(3), Hughes J(3), Fourie B(3), Nielsen J(4),

Garcia-Prats AJ(#)(3)(5), Savic RM(#)(1).

Rifampicin-resistant tuberculosis (RR-TB) involves treatment with many drugs that can prolong the QT interval; this risk may increase when multiple QT-prolonging drugs are used together. We assessed QT interval prolongation in children with RR-TB receiving one or more QT-prolonging drugs. Data were obtained from two prospective observational studies in Cape Town, South Africa. Electrocardiograms were performed before and after drug administration of clofazimine (CFZ), levofloxacin (LFX), moxifloxacin (MFX), bedaquiline (BDQ), and delamanid. The change in Fridericia-corrected QT (QTcF) was modeled. Drug and other covariate effects were quantified. A total of 88 children with a median (2.5th-to-97.5th range) age of 3.9 (0.5 to 15.7) years were included, of whom 55 (62.5%) were under 5 years of age. A QTcF interval of >450 ms was observed in 7 patient-visits: regimens were CFZ+MFX (n = 3), CFZ+BDQ+LFX (n = 2), CFZ alone (n = 1), and MFX alone (n = 1). There were no events with a QTcF interval of >500 ms. In a multivariate analysis, CFZ+MFX was associated with a 13.0-ms increase in change in QTcF ($P < 0.001$) and in maximum QTcF ($P = 0.0166$) compared to those when other MFX- or LFX-based regimens were used. In conclusion, we found a low risk of QTcF interval prolongation in children with RR-TB who received at least one QT-prolonging drug. Greater increases in maximum QTcF and ΔQTcF were observed when MFX and CFZ were used together. Future studies characterizing exposure-QTcF responses in children will be helpful to ensure safety with higher doses if required for effective treatment of RR-TB.

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PMCID: PMC10353402
PMID: 37358463 [Indexed for MEDLINE]

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

5. What clinic closure reveals about care for drug-resistant TB: a qualitative study.

BMC Infect Dis. 2023 Jul 17;23(1):474. doi: 10.1186/s12879-023-08405-7.

Govender T(1), Furin JJ(2), Edwards A(3)(4), Pillay S(5), Murphy RA(6)(7).

BACKGROUND: There have been calls for "person-centered" approaches to drug-resistant tuberculosis (DR-TB) care. In 2020, Charles James Hospital in South Africa, which incorporated person-centered care, was closed. Patients were referred mid-course to a centralized, tertiary hospital, providing an opportunity to examine person-centered DR-TB and HIV care from the perspective of patients who lost access to it.

METHODS: The impact of transfer was explored through qualitative interviews performed using standard methods. Analysis involved grounded theory; interviews were assessed for theme and content.
RESULTS: After switching to the centralized site, patients reported being unsatisfied with losing access to a single clinic and pharmacy where DR-TB, HIV and chronic disease care were integrated. Patients also reported a loss of care continuity; at the decentralized site there was a single, familiar clinician whereas the centralized site had multiple, changing clinicians and less satisfactory communication. Additionally, patients reported more disease-related stigma and less respectful treatment, noting the loss of a "special place" for DR-TB treatment.
CONCLUSION: By focusing on a DR-TB clinic closure, we uncovered aspects of person-centered care that were critical to people living with DR-TB and HIV. These perspectives can inform how care for DR-TB is operationalized to optimize treatment retention and effectiveness.

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PMCID: PMC10353129
PMID: 37460960 [Indexed for MEDLINE]

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

6. Treatment cascade for patients with multidrug- or rifampicin-resistant tuberculosis and associated factors with patient attrition in southeastern China: a retrospective cohort study.

J Infect Public Health. 2023 Jul;16(7):1073-1080. doi: 10.1016/j.jiph.2023.05.012. Epub 2023 May 12.

Chen B(1), Chen X(2), Ren Y(3), Peng Y(2), Wang F(2), Zhou L(2), Xu B(4).

OBJECTIVES: To address gaps in health services for multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB), a treatment cascade model was used to evaluate patient retention and attrition at each successive step required to achieve a successful treatment outcome.
METHODS: From 2015-2018, a four-step treatment cascade model was established in patients with confirmed MDR/RR-TB in southeast China. Step 1: diagnosis of MDR/RR-TB, step 2: Initiation of treatment, step 3: still under treatment at 6 month and step 4: cure or completion of MDR/RR-TB treatment, with each

successive step including a gap that shows attrition of patients between steps. The retention and attrition of each step were graphed. Multi-variate logistic regression was carried out to further identify potential factors associated with the attrition.
RESULTS: In the treatment cascade consisting of 1752 MDR/RR-TB patients, the overall patient attrition rate was 55.8% (978/1752), with 28.0% (491/1752), 19.9% (251/1261), and 23.4% (236/1010) of patients attrition in the first, second, and third gap. Factors associated with MDR/RR-TB patients not initiating treatment included age ≥60 years (OR:2.875), and time for diagnosis ≥30 days (OR: 2.653). Patients who were diagnosed with MDR/RR-TB through rapid molecular test (OR: 0.517) and non-migrant residents of Zhejiang Province (OR: 0.273) both exhibited a lower likelihood of attrition during the treatment initiation phase. Meanwhile, old age (OR: 2.190) and non-resident migrants to the province were factors associated with not completing ≥ 6 months of treatment. Old age (OR: 3.883), retreatment (OR: 1.440), and time to diagnosis ≥30 days (OR: 1.626) were factors contributing to poor treatment outcomes.
CONCLUSION: Several programmatic gaps were identified in the MDR/RR-TB treatment cascade. Future policies should provide more comprehensive support for vulnerable populations to improve the care quality at each step.

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PMID: 37209611 [Indexed for MEDLINE]

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

7. To Test or Not? Xpert MTB/RIF as an Alternative to Smear Microscopy to Guide Line Probe Assay Testing for Drug-Resistant Tuberculosis.

J Clin Microbiol. 2023 Jul 20;61(7):e0001723. doi: 10.1128/jcm.00017-23. Epub 2023 Jun 27.

Pillay S(1)(2), de Vos M(1), Sohn H(3), Ghebrekristos Y(2), Dolby T(2), Warren RM(1), Theron G(1).

Xpert MTB/RIF (Xpert) revolutionized tuberculosis (TB) diagnosis. Laboratory decision making on whether widely-used reflex drug susceptibility assays (MTBDRplus, first-line resistance; MTBDRsl, second-line) are conducted is based on smear status, with smear-negative specimens often excluded. We performed receiver operator characteristic (ROC) curve analyses using bacterial load information (smear microscopy grade, Xpert-generated semi-quantitation

categories and minimum cycle threshold [CTmin] values) from Xpert rifampicin-resistant sputum for the prediction of downstream line probe assay results as "likely non-actionable" (no resistance or susceptible results generated). We evaluated actionable-to-non-actionable result ratios and pay-offs with missed resistance versus LPAs done universally. Smear-negatives were more likely than smear-positive specimens to generate a non-actionable MTBDRplus (23% [133/559] versus 4% [15/381]) or MTBDRsl (39% [220/559] versus 12% [47/381]) result. However, excluding smear-negatives would result in missed rapid diagnoses (e.g., only 49% [264/537] of LPA-diagnosable isoniazid resistance would be detected if smear-negatives were omitted). Testing smear-negatives with a semi-quantitation category ≥ "medium" had a high ratio of actionable-to-non-actionable results (12.8 or a 4-fold improvement versus testing all using MTBDRplus, 4.5 or 3-fold improvement for MTBDRsl), which would still capture 64% (168/264) and 77% (34/44) of LPA-detectable smear-negative resistance, respectively. Use of CTmins permitted optimization of this ratio with higher specificity for non-actionable results but decreased resistance detected. Xpert quantitative information permits identification of a smear-negative subset in whom the payoffs of the ratio of actionable-to-non-actionable LPA results with missed resistance may prove acceptable to laboratories, depending on context. Our findings permit the rational expansion of direct DST to certain smear-negative sputum specimens.

DOI: 10.1128/jcm.00017-23
PMID: 37367228

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

8. Simultaneous screening for COVID-19 and tuberculosis, India.

Bull World Health Organ. 2023 Jul 1;101(7):445-452. doi: 10.2471/BLT.22.288960. Epub 2023 May 18.

Duppala K(1), Sen R(1), Shenai S(1), Gomare M(2), Shah D(2), Tipre P(2), Joshi M(3), Chowdhury J(3), Chadha SS(1), Sarin S(1).

OBJECTIVE: To evaluate the implementation of new operational workflows for simultaneous screening of coronavirus disease 2019 (COVID-19) and tuberculosis at four high-volume COVID-19 testing centres located in tertiary hospitals in Mumbai, India.
METHODS: Each centre already offering antigen-detecting rapid diagnostic tests were equipped with a rapid molecular testing platform for COVID-19 and tuberculosis, sufficient laboratory staff, and reagents and consumables for screening. Using a verbal tuberculosis questionnaire, a patient follow-up agent

screened individuals visiting the COVID-19 testing centres. Presumptive tuberculosis patients were asked to provide sputum samples for rapid molecular testing. Subsequently, we reversed our operational workflow to also screen patients visiting tuberculosis outpatient departments for COVID-19, using rapid diagnostic tests.
RESULTS: From March to December 2021, we screened 14 588 presumptive COVID-19 patients for tuberculosis, of whom 475 (3.3%) were identified as having presumptive tuberculosis. Of these, 288 (60.6%) were tested and 32 individuals (11.1%) were identified as tuberculosis positive (219 cases per 100 000 individuals screened). Of the tuberculosis-positive individuals, three had rifampicin-resistant tuberculosis. Among the remaining 187 presumptive tuberculosis cases not tested, 174 reported no symptoms at follow-up and 13 individuals either refused testing or could not be traced. Of the 671 presumptive tuberculosis cases screened for COVID-19, 17 (2.5%) were positive by antigen rapid diagnostic tests, and five (0.7%) who tested negative, later tested positive on the molecular testing platform (2483 COVID-19 cases per 100 000 individuals screened).
CONCLUSION: Simultaneous screening for COVID-19 and tuberculosis in India is operationally feasible and can improve real-time on-site detection of COVID-19 and tuberculosis.

DOI: 10.2471/BLT.22.288960
PMCID: PMC10300779
PMID: 37397177 [Indexed for MEDLINE]

9. Linezolid resistance in patients with drug-resistant TB.

Int J Tuberc Lung Dis. 2023 Jul 1;27(7):567-569. doi: 10.5588/ijtld.22.0632.

Vengurlekar D(1), Walker C(2), Mahajan R(3), Dalal A(4), Chavan V(1), Galindo MA(1), Iyer A(1), Mansoor H(1), Silsarma A(1), Isaakidis P(5), Spencer H(6).

DOI: 10.5588/ijtld.22.0632
PMCID: PMC10321363
PMID: 37353865 [Indexed for MEDLINE]

10. Impact of Anti-Tuberculosis Drug Use on Treatment Outcomes in Patients with Pulmonary Fluoroquinolone-Resistant Multidrug-Resistant Tuberculosis: A Nationwide Retrospective Cohort Study with Propensity Score Matching.

Tuberc Respir Dis (Seoul). 2023 Jul;86(3):234-244. doi: 10.4046/trd.2023.0040.

Epub 2023 May 31.

Choi H(1), Jeong D(2), Kang YA(3), Jeon D(4), Kang HY(5), Kim HJ(6), Kim HS(7), Mok J(8)(9).

BACKGROUND: Effective treatment of fluoroquinolone-resistant multidrug-resistant tuberculosis (FQr-MDR-TB) is difficult because of the limited number of available core anti-TB drugs and high rates of resistance to anti-TB drugs other than FQs. However, few studies have examined anti-TB drugs that are effective in treating patients with FQr-MDR-TB in a real-world setting.
METHODS: The impact of anti-TB drug use on treatment outcomes in patients with pulmonary FQr-MDR-TB was retrospectively evaluated using a nationwide integrated TB database (Korean Tuberculosis and Post-Tuberculosis). Data from 2011 to 2017 were included.
RESULTS: The study population consisted of 1,082 patients with FQr-MDR-TB. The overall treatment outcomes were as follows: treatment success (69.7%), death (13.7%), lost to follow-up or not evaluated (12.8%), and treatment failure (3.9%). On a propensity-score-matched multivariate logistic regression analysis, the use of bedaquiline (BDQ), linezolid (LZD), levofloxacin (LFX), cycloserine (CS), ethambutol (EMB), pyrazinamide, kanamycin (KM), prothionamide (PTO), and para-aminosalicylic acid against susceptible strains increased the treatment success rate (vs. unfavorable outcomes). The use of LFX, CS, EMB, and PTO against susceptible strains decreased the mortality (vs. treatment success).
CONCLUSION: A therapeutic regimen guided by drug-susceptibility testing can improve the treatment of patients with pulmonary FQr-MDR-TB. In addition to core anti-TB drugs, such as BDQ and LZD, treatment of susceptible strains with later-generation FQs and KM may be beneficial for FQr-MDR-TB patients with limited treatment options.

DOI: 10.4046/trd.2023.0040
PMCID: PMC10323203
PMID: 37254489

Conflict of interest statement: Conflicts of Interest No potential conflict of interest relevant to this article was reported.

11. Cost of treatment support for multidrug-resistant tuberculosis using patient-centred approaches in Ethiopia: a model-based method.

Infect Dis Poverty. 2023 Jul 7;12(1):65. doi: 10.1186/s40249-023-01116-w.

Rosu L(1), Morgan L(2), Tomeny EM(3), Worthington C(2), Jin M(2), Nidoi J(4), Worthington D(2).

BACKGROUND: Patient and health system costs for treating multidrug-resistant tuberculosis (MDR-TB) remain high even after treatment duration was shortened. Many patients do not finish treatment, contributing to increased transmission and antimicrobial resistance. A restructure of health services, that is more patient-centred has the potential to reduce costs and increase trust and patient satisfaction. The aim of the study is to investigate how costs would change in the delivery of MDR-TB care in Ethiopia under patient-centred and hybrid approaches compared to the current standard-of-care.
METHODS: We used published data, collected from 2017 to 2020 as part of the Standard Treatment Regimen of Anti-Tuberculosis Drugs for Patients with MDR-TB (STREAM) trial, to populate a discrete event simulation (DES) model. The model was developed to represent the key characteristics of patients' clinical pathways following each of the three treatment delivery strategies. To the pathways of 1000 patients generated by the DES model we applied relevant patient cost data derived from the STREAM trial. Costs are calculated for treating patients using a 9-month MDR-TB treatment and are presented in 2021 United States dollars (USD).
RESULTS: The patient-centred and hybrid strategies are less costly than the standard-of-care, from both a health system (by USD 219 for patient-centred and USD 276 for the hybrid strategy) and patient perspective when patients do not have a guardian (by USD 389 for patient-centred and USD 152 for the hybrid strategy). Changes in indirect costs, staff costs, transport costs, inpatient stay costs or changes in directly-observed-treatment frequency or hospitalisation duration for standard-of-care did not change our results.
CONCLUSION: Our findings show that patient-centred and hybrid strategies for delivering MDR-TB treatment cost less than standard-of-care and provide critical evidence that there is scope for such strategies to be implemented in routine care. These results should be used inform country-level decisions on how MDR-TB is delivered and also the design of future implementation trials.

DOI: 10.1186/s40249-023-01116-w
PMCID: PMC10327382
PMID: 37420269 [Indexed for MEDLINE]

Conflict of interest statement: Authors have no competing interests to declare.

12. Pharmacogenetics as part of recommended precision medicine for tuberculosis treatment in African populations: Could it be a reality?

Clin Transl Sci. 2023 Jul;16(7):1101-1112. doi: 10.1111/cts.13520. Epub 2023 Jun

8.

Oelofse C(1), Ndong Sima CAA(1), Möller M(1)(2), Uren C(1)(2).

Globally, tuberculosis (TB) is the second most lethal infectious disease. However, in sub-Saharan Africa, TB has the largest disease burden, with drug-resistant TB increasingly becoming a concern. The social and economic impact of TB should not be overlooked, especially in areas where healthcare systems are overburdened, and resources need to be allocated judiciously. The aim of pharmacogenetics (PGx) is to improve therapeutic response and to minimize adverse drug reactions by selecting the most optimal drug and dosage for the individual patient. Implementation of PGx into routine clinical care has been slow, especially in resource-limited settings, because of perceived high costs relative to uncertain benefit. Given the impact of TB on the disease and disability burden in these regions, a better understanding and optimization of TB treatment in understudied African populations is vital. The first weeks of treatment are the most crucial for treatment success, and a point-of-care pre-emptive PGx test could start patients on the most bactericidal and least toxic drug combination. This may potentially reduce the number of patients returning to clinical care and streamline the use of limited resources across the healthcare system. This review explores the status of TB PGx in Africa, the utility of existing TB PGx testing panels, and the economic feasibility in developing a clinically valuable, cost-effective, pre-emptive PGx test to guide optimized, new dosing regimens specifically for African population groups. TB is a disease of poverty, but investment in PGx research in African populations could ensure improved treatments and long-term cost savings.

DOI: 10.1111/cts.13520
PMCID: PMC10339705
PMID: 37291686 [Indexed for MEDLINE]

Conflict of interest statement: The authors declared no competing interests for this work.

13. Using Microfluidic Chip and Allele-Specific PCR to Rapidly Identify Drug Resistance-Associated Mutations of Mycobacterium tuberculosis.

Infect Drug Resist. 2023 Jul 3;16:4311-4323. doi: 10.2147/IDR.S410779.
eCollection 2023.

Chen S(1), Liu H(1), Li T(1), Lai W(1), Liu L(1), Xu Y(2), Qu J(1).

BACKGROUND: The currently used conventional susceptibility testing for drug-resistant Mycobacterium tuberculosis (M.TB) is limited due to being time-consuming and having low efficiency. Herein, we propose the use of a microfluidic-based method to rapidly detect drug-resistant gene mutations using Kompetitive Allele-Specific PCR (KASP).
METHODS: A total of 300 clinical samples were collected, and DNA extraction was performed using the "isoChip®" Mycobacterium detection kit. Phenotypic susceptibility testing and Sanger sequencing were performed to sequence the PCR products. Allele-specific primers targeting 37 gene mutation sites were designed, and a microfluidic chip (KASP) was constructed using 112 reaction chambers to simultaneously detect multiple mutations. Chip validation was performed using clinical samples.
RESULTS: Phenotypic susceptibility of clinical isolates revealed 38 rifampicin (RIF)-resistant, 64 isoniazid (INH)-resistant, 48 streptomycin (SM)-resistant and 23 ethambutol (EMB)-resistant strains, as well as 33 multi-drug-resistant TB (MDR-TB) strains and 20 strains fully resistant to all four drugs. Optimization of the chip-based detection system for drug resistance detection showed satisfactory specificity and maximum fluorescence at a DNA concentration of 1×101 copies/μL. Further analysis revealed that 76.32% of the RIF-resistant strains harbored rpoB gene mutations (sensitivity, 76.32%; specificity 100%), 60.93% of the INH-resistant strains had katG gene mutations (sensitivity, 60.93%; specificity, 100%), 66.66% of the SM-resistant strains carried drug resistance gene mutations (sensitivity, 66.66%; specificity, 99.2%), and 69.56% of the EMB-resistant strains had embB gene mutations (sensitivity, 69.56%; specificity, 100%). Further, the overall agreement between the microfluidic chip and Sanger sequencing was satisfactory, with a turnaround time of the microfluidic chip was approximately 2 hours, much shorter than the conventional DST method.
CONCLUSION: The proposed microfluidic-based KASP assay provides a cost-effective and convenient method for detecting mutations associated with drug resistance in M. tuberculosis. It represents a promising alternative to the traditional DST method, with satisfactory sensitivity and specificity and a much shorter turnaround time.

DOI: 10.2147/IDR.S410779
PMCID: PMC10327919
PMID: 37424666

Conflict of interest statement: The authors report no conflicts of interest in

this work.

14. Mapping Research Trends of Medications for Multidrug-Resistant Pulmonary Tuberculosis Based on the Co-Occurrence of Specific Semantic Types in the MeSH Tree: A Bibliometric and Visualization-Based Analysis of PubMed Literature (1966-2020).

Drug Des Devel Ther. 2023 Jul 10;17:2035-2049. doi: 10.2147/DDDT.S409604. eCollection 2023.

Xu S(1), Fu Y(2), Xu D(1), Han S(1), Wu M(3), Ju X(1), Liu M(1), Huang DS(4)(5), Guan P(4)(6).

BACKGROUND: Before the COVID-19 pandemic, tuberculosis is the leading cause of death from a single infectious agent worldwide for the past 30 years. Progress in the control of tuberculosis has been undermined by the emergence of multidrug-resistant tuberculosis. The aim of the study is to reveal the trends of research on medications for multidrug-resistant pulmonary tuberculosis (MDR-PTB) through a novel method of bibliometrics that co-occurs specific semantic Medical Subject Headings (MeSH).
METHODS: PubMed was used to identify the original publications related to medications for MDR-PTB. An R package for text mining of PubMed, pubMR, was adopted to extract data and construct the co-occurrence matrix-specific semantic types. Biclustering analysis of high-frequency MeSH term co-occurrence matrix was performed by gCLUTO. Scientific knowledge maps were constructed by VOSviewer to create overlay visualization and density visualization. Burst detection was performed by CiteSpace to identify the future research hotspots.
RESULTS: Two hundred and eight substances (chemical, drug, protein) and 147 diseases related to MDR-PTB were extracted to form a specific semantic co-occurrence matrix. MeSH terms with frequency greater than or equal to six were selected to construct high-frequency co-occurrence matrix (42 × 20) of specific semantic types contains 42 substances and 20 diseases. Biclustering analysis divided the medications for MDR-PTB into five clusters and reflected the characteristics of drug composition. The overlay map indicated the average age gradients of 42 high-frequency drugs. Fifteen top keywords and 37 top terms with the strongest citation bursts were detected.
CONCLUSION: This study evaluated the literatures related to MDR-PTB drug therapy, providing a co-occurrence matrix model based on the specific semantic types and a new attempt for text knowledge mining. Compared with the macro knowledge structure or hot spot analysis, this method may have a wider scope of application and a more in-depth degree of analysis.

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PMCID: PMC10348322
PMID: 37457889 [Indexed for MEDLINE]

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

15. Mortality rate and associated factors among patients co-infected with drug resistant tuberculosis/HIV at Mulago National Referral Hospital, Uganda, a retrospective cohort study.

PLOS Glob Public Health. 2023 Jul 6;3(7):e0001020. doi: 10.1371/journal.pgph.0001020. eCollection 2023.

Bayowa JR(1), Kalyango JN(1), Baluku JB(2), Katuramu R(3), Ssendikwanawa E(1), Zalwango JF(1), Akunzirwe R(1), Nanyonga SM(1), Amutuhaire JS(1), Muganga RK(1), Cherop A(1).

Drug resistant tuberculosis (DR-TB)/HIV co-infection remains a growing threat to public health and threatens global TB and HIV prevention and care programs. HIV is likely to worsen the outcomes of DR-TB and DR-TB is likely to worsen the outcomes of HIV despite the scale up of TB and HIV services and advances in treatment and diagnosis. This study determined the mortality rate and factors associated with mortality among persons on treatment co-infected with drug resistant TB and HIV at Mulago National Referral Hospital. We retrospectively reviewed data of 390 persons on treatment that had a DR-TB/HIV co-infection in Mulago National Referral Hospital from January 2014 to December 2019.Modified poisson regression with robust standard errors was used to determine relationships between the independent variables and the dependent variable (mortality) at bivariate and multivariate analysis. Of the 390 participants enrolled, 201(53.9%) were males with a mean age of 34.6 (±10.6) and 129 (33.2%,95% CI = 28.7-38.1%) died. Antiretroviral therapy(ART) initiation (aIRR 0.74, 95% CI = 0.69-0.79), having a body mass index (BMI)≥18.5Kg/m2 (aIRR 1.01, 95% CI = 1.03-1.17), having a documented client phone contact (aIRR 0.85, 95% CI = 0.76-0.97), having a mid-upper arm circumference,(MUAC) ≥18.5cm (aIRR 0.90, 95% CI = 0.82-0.99), being on first and second line ART regimen (aIRR 0.83, 95% CI = 0.77-0.89),having a known viral load (aIRR 1.09, 95% CI = 1.00-1.21) and having an adverse event during the course of treatment (aIRR 0.88, 95% CI = 0.83-0.93) were protective against mortality. There was a significantly high mortality rate due to DR-TB/HIV co-infection. These results suggest that initiation of all persons living with HIV/AIDS (PLWHA) with DR-TB on ART and frequent monitoring of adverse drug events highly reduces mortality.

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PMID: 37410761

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

16. Estimating the prevalence of poor-quality anti-TB medicines: a neglected risk for global TB control and resistance.

BMJ Glob Health. 2023 Jul;8(7):e012039. doi: 10.1136/bmjgh-2023-012039.

Tabernero P(1)(2)(3)(4), Newton PN(2)(3)(4).

OBJECTIVES: Tuberculosis (TB) remains a major global public health problem, especially with the recent emergence of multidrug-resistant TB and extensively drug-resistant TB. There has been little consideration of the extent of substandard and falsified (SF) TB medicines as drivers of resistance. We assessed the evidence on the prevalence of SF anti-TB medicines and discussed their public health impact.
MATERIALS/METHODS: We searched Web of Science, Medline, Pubmed, Google Scholar, WHO, US Pharmacopeia and Medicines Regulatory Agencies websites for publications on anti-TB medicines quality up to 31 October 2021. Publications reporting on the prevalence of SF anti-TB drugs were evaluated for quantitative analysis.
RESULTS: Of the 530 screened publications, 162 (30.6%) were relevant to anti-TB medicines quality; of those, 65 (40.1%) described one or more TB quality surveys in a specific location or region with enough information to yield an estimate of the local prevalence of poor-quality TB medicines. 7682 samples were collected in 22 countries and of those, 1170 (15.2%) failed at least one quality test. 14.1% (879/6255) of samples failed in quality surveys, 12.5% (136/1086) in bioequivalence studies and 36.9% (87/236) in accelerated biostability studies. The most frequently assessed were rifampicin monotherapy (45 studies, 19.5%) and isoniazid monotherapy (33, 14.3%), rifampicin-isoniazid-pyrazinamide-ethambutol fixed dose combinations (28, 12.1%) and rifampicin-isoniazid (20, 8.6%). The median (IQR) number of samples collected per study was 12 (1-478).
CONCLUSIONS: SF, especially substandard, anti-TB medicines are present worldwide. However, TB medicine quality data are few and are therefore not generalisable that 15.2% of global anti-TB medicine supply is SF. The evidence

available suggests that the surveillance of the quality of TB medicines needs to be an integral part of treatment programmes. More research is needed on the development and evaluation of rapid, affordable and accurate portable devices to empower pharmacy inspectors to screen for anti-TB medicines.

DOI: 10.1136/bmjgh-2023-012039
PMCID: PMC10347509
PMID: 37433693 [Indexed for MEDLINE]

Conflict of interest statement: Competing interests: None declared.

17. Effect of compensatory evolution in the emergence and transmission of rifampicin-resistant Mycobacterium tuberculosis in Cape Town, South Africa: a genomic epidemiology study.

Lancet Microbe. 2023 Jul;4(7):e506-e515. doi: 10.1016/S2666-5247(23)00110-6. Epub 2023 Jun 6.

Goig GA(1), Menardo F(2), Salaam-Dreyer Z(3), Dippenaar A(4), Streicher EM(5), Daniels J(6), Reuter A(6), Borrell S(7), Reinhard M(7), Doetsch A(7), Beisel C(8), Warren RM(5), Cox H(9), Gagneux S(7).

BACKGROUND: Experimental data show that drug-resistance-conferring mutations are often associated with a decrease in the replicative fitness of bacteria in vitro, and that this fitness cost can be mitigated by compensatory mutations; however, the role of compensatory evolution in clinical settings is less clear. We assessed whether compensatory evolution was associated with increased transmission of rifampicin-resistant tuberculosis in Khayelitsha, Cape Town, South Africa.
METHODS: We did a genomic epidemiological study by analysing available M tuberculosis isolates and their associated clinical data from individuals routinely diagnosed with rifampicin-resistant tuberculosis in primary care and hospitals in Khayelitsha, Cape Town, South Africa. Isolates were collected as part of a previous study. All individuals diagnosed with rifampicin-resistant tuberculosis and with linked biobanked specimens were included in this study. We applied whole-genome sequencing, Bayesian reconstruction of transmission trees, and phylogenetic multivariable regression analysis to identify individual and bacterial factors associated with the transmission of rifampicin-resistant M tuberculosis strains.
FINDINGS: Between Jan 1, 2008, and Dec 31, 2017, 2161 individuals were diagnosed

with multidrug-resistant or rifampicin-resistant tuberculosis in Khayelitsha, Cape Town, South Africa. Whole-genome sequences were available for 1168 (54%) unique individual M tuberculosis isolates. Compensatory evolution was associated with smear-positive pulmonary disease (adjusted odds ratio 1·49, 95% CI 1·08-2·06) and a higher number of drug-resistance-conferring mutations (incidence rate ratio 1·38, 95% CI 1·28-1·48). Compensatory evolution was also associated with increased transmission of rifampicin-resistant disease between individuals (adjusted odds ratio 1·55; 95% CI 1·13-2·12), independent of other patient and bacterial factors.
INTERPRETATION: Our findings suggest that compensatory evolution enhances the in vivo fitness of drug-resistant M tuberculosis genotypes, both within and between patients, and that the in vitro replicative fitness of rifampicin-resistant M tuberculosis measured in the laboratory correlates with the bacterial fitness measured in clinical settings. These results emphasise the importance of enhancing surveillance and monitoring efforts to prevent the emergence of highly transmissible clones capable of rapidly accumulating new drug resistance mutations. This concern becomes especially crucial at present, because treatment regimens incorporating novel drugs are being implemented.
FUNDING: Funding for this study was provided by a Swiss and South Africa joint research award (grant numbers 310030_188888, CRSII5_177163, and IZLSZ3_170834), the European Research Council (grant number 883582), and a Wellcome Trust fellowship (to HC; reference number 099818/Z/12/Z). ZS-D was funded through a PhD scholarship from the South African National Research Foundation and RMW was funded through the South African Medical Research Council.

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PMCID: PMC10319636
PMID: 37295446 [Indexed for MEDLINE]

Conflict of interest statement: Declaration of interest RMW acknowledges baseline support from the South African Medical Research Council. All other authors declare no competing interests.

18. Feature weighted models to address lineage dependency in drug-resistance prediction from Mycobacterium tuberculosis genome sequences.

Bioinformatics. 2023 Jul 1;39(7):btad428. doi: 10.1093/bioinformatics/btad428.

Billows N(1)(2), Phelan JE(3), Xia D(1), Peng Y(4), Clark TG(3)(5), Chang YM(1).

MOTIVATION: Tuberculosis (TB) is caused by members of the Mycobacterium tuberculosis complex (MTBC), which has a strain- or lineage-based clonal population structure. The evolution of drug-resistance in the MTBC poses a threat to successful treatment and eradication of TB. Machine learning approaches are being increasingly adopted to predict drug-resistance and characterize underlying mutations from whole genome sequences. However, such approaches may not generalize well in clinical practice due to confounding from the population structure of the MTBC.
RESULTS: To investigate how population structure affects machine learning prediction, we compared three different approaches to reduce lineage dependency in random forest (RF) models, including stratification, feature selection, and feature weighted models. All RF models achieved moderate-high performance (area under the ROC curve range: 0.60-0.98). First-line drugs had higher performance than second-line drugs, but it varied depending on the lineages in the training dataset. Lineage-specific models generally had higher sensitivity than global models which may be underpinned by strain-specific drug-resistance mutations or sampling effects. The application of feature weights and feature selection approaches reduced lineage dependency in the model and had comparable performance to unweighted RF models.
AVAILABILITY AND IMPLEMENTATION: https://github.com/NinaMercedes/RF_lineages.

DOI: 10.1093/bioinformatics/btad428
PMCID: PMC10351970
PMID: 37428143 [Indexed for MEDLINE]

Conflict of interest statement: None declared.

19. GeneXpert MTB/RIF Ultra performance to detect uncommon rpoB mutations in Mycobacterium tuberculosis.

BMC Res Notes. 2023 Jul 14;16(1):146. doi: 10.1186/s13104-023-06394-z.

Rigouts L(1), Keysers J(2), Rabab R(2), Fissette K(2), van Deun A(3), de Jong BC(2).

OBJECTIVE: To investigate the performance of GeneXpert MTB/RIF Ultra to accurately detect rifampicin resistance for less common rpoB mutations that potentially confer phenotypic resistance, we tested 28 such Mycobacterium tuberculosis cultures with Xpert Ultra.
RESULTS: They represented 22 different (combinations of) rpoB mutations. Of 28

isolates tested, one was reported by Xpert Ultra as "No rifampicin resistance detected", 8 yielded a "Rifampicin indeterminate" result, and 19 were identified as rifampicin resistant. Overall, our results corroborate previous observations on the "Indeterminate" results for mutations at codon 432, while we add Lys446Gln as additional "Indeterminate" result and Pro439Leu as a false rifampicin-susceptible result. Furthermore, we document other uncommon point mutations and indels across the rpoB gene that are mostly correctly identified as rifampicin resistant by Xpert ultra (V3). Taken together, "Indeterminate" results in Xpert Ultra may indicate underlying rpoB mutations within the rifampicin-resistance determining region and thus increase the post-test probability of rifampicin resistance, albeit to an unknown extent.

DOI: 10.1186/s13104-023-06394-z
PMCID: PMC10347863
PMID: 37452349 [Indexed for MEDLINE]

Conflict of interest statement: None of the authors have competing interests with the commercial test/company under investigation.

20. [Analysis of Mycobacterium tuberculosis Complex Strains Isolated from the Samples of Patients Living in Northern Syria].

Mikrobiyol Bul. 2023 Jul;57(3):444-453. doi: 10.5578/mb.20239936.

Gazel D(1), Çeylan K(1), Çalışkantürk G(2), Karslıgil T(1).

Tuberculosis causes serious mortality and morbidity worldwide each year. A lot of effort and money is spent for the diagnosis and treatment of tuberculosis all over the world. The importance that countries give to health policies and public health is inversely proportional to the incidence of tuberculosis and multidrug resistant tuberculosis. The aim of our study was to evaluate the resistance profiles of Mycobacterium tuberculosis complex strains which were isolated from sputum samples, collected by World Health Organisation from patients living in the northern region of Syria, where health services were disrupted due to the civil war. According to the protocol signed between the World Health Organization and our hospital; sputum samples taken from tuberculosis patients living in Afrin, Azez and Idlib regions or suspected of being resistant to anti-tuberculosis drugs were studied in our hospital. The cultivation process was performed in our laboratory using Löwenstein Jensen media and MGIT-960 system. The susceptibility tests for primary anti-tuberculosis drugs were performed using MGIT-960 system for M.tuberculosis complex isolates. The

isolates identified as MDR/RD-TB (multi-drug-resistant-rifampicin-resistant tuberculosis) were sent to National Tuberculosis Reference Laboratory of Public Health Institution of Türkiye for susceptibility testing to first and second line drugs. Mutation and wild-type determination were studied by "Line Probe Assay (LPA)" method to investigate the susceptibility of the isolates to isoniazid, rifampicin, fluoroquinolone and aminoglycoside/cyclic peptide. The results obtained from the patients were collected and evaluated retrospectively from the records. Growth was observed in 18 samples out of 171 sputum samples from 67 patients; 13 isolates were detected as MDR-TB while one isolate was detected as mono RR-TB. The rate of mono RR-TB was 1.5% and the rate of MDR-TB was 19.4%. MUT3 causing rifampicin resistance was detected in 17.9% of the patients, katG/MUT1 causing isoniazid resistance in 17.9% and WT loss causing aminoglycoside/cyclic peptide resistance were detected in 19.4% of the patients. Neither fluoroquinolone resistance nor a mutation leading to fluoroquinolone resistance was detected in the study. When the sputum samples taken from the patients living in Northern Syria were examined, the frequency of MDR-TB was found to be quite high. MDR-TB, which is an important public health problem, was found at high rates due to the internal turmoil in the region and poor accessibility to health services. Since the gene mutations causing drug resistance with the LPA method differ with the conducted studies, it is important to evaluate the dominant gene mutations for determining the TB treatment strategies in the region.

DOI: 10.5578/mb.20239936
PMID: 37462307 [Indexed for MEDLINE]

PubMed Non-Open Access

21. Comprehensive coverage on anti-mycobacterial endeavour reported during 2022.

Eur J Med Chem. 2023 Jul 5;255:115409. doi: 10.1016/j.ejmech.2023.115409. Epub 2023 Apr 21.

Dhameliya TM(1), Vekariya DD(2), Patel HY(2), Patel JT(2).

TB being one of the deadliest diseases and second most common infectious cause of deaths, poses the severe threat to global health. The extended duration of therapy owing to resistance and its upsurge in immune-compromised patients have been the driving force for the development of novel of anti-TB scaffolds. Recently, we have compiled the account of anti-mycobacterial scaffolds published during 2015-2020 and updated them in 2021. The present work involves the insights on the anti-mycobacterial scaffolds reported in 2022 with their mechanism of action, structure activity relationships, along with the key perceptions for the design of newer anti-TB agents for the broader interests of

medicinal chemists.

DOI: 10.1016/j.ejmech.2023.115409
PMID: 37120997 [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.

22. [Treatment of tuberculosis: what is new?].

Inn Med (Heidelb). 2023 Jul;64(7):701-707. doi: 10.1007/s00108-023-01523-z. Epub 2023 Jun 14.

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

Brehm TT(1)(2), Köhler N(3), Schmiedel S(1)(2), Terhalle E(4), Martensen J(5), Kalsdorf B(3), Kandulla J(6), Heyckendorf J(7), Kuhns M(8), Friesen I(8), Lange C(9)(10)(11)(12).

Never before have so many people around the world been simultaneously affected by tuberculosis. Tuberculosis is the leading cause of death from a bacterial infectious disease worldwide. The World Health Organization's ambitious goal from 2014 of achieving global elimination of tuberculosis does not seem realistic, but on current trends, tuberculosis could be eliminated in the European Union by 2040. Since the beginning of 2022, there have been more innovations for the treatment of tuberculosis than in no other comparable time period before. One month of rifapentine and isoniazid is effective in treating latent tuberculosis infection. However, rifapentine is licensed in the USA but not in the EU and must be imported for individual cases. The duration of the standard treatment for tuberculosis can be shortened to four months but this treatment regimen is also based on rifapentine, in addition to isoniazid, pyrazinamide, and moxifloxacin. The approval of rifapentine in Europe is a much-needed step towards shortening the treatment of tuberculosis. With new drugs an even shorter standard treatment of only 2 months is possible. The treatment of multidrug-resistant/rifampicin-resistant tuberculosis (MDR-/RR-TB) has been shortened to six months, the same length as the standard treatment available in Germany. The combination of bedaquiline, pretomanid, linezolid ± moxifloxacin, cured around 90% of affected patients were cured in studies with a treatment duration of six months. With 19 drugs in clinical trials, the treatment of tuberculosis is expected to continue to improve rapidly

in the coming years.

DOI: 10.1007/s00108-023-01523-z
PMID: 37316702 [Indexed for MEDLINE]

23. Stress resilience in patients with drug-resistant TB.

Int J Tuberc Lung Dis. 2023 Jul 1;27(7):551-556. doi: 10.5588/ijtld.22.0648.

Nur N(1), Sharif AB(2), Mitra DK(1).

BACKGROUND: The worldwide increase in drug-resistant pulmonary TB (DR-PTB) has a significant impact on patient´s physical and mental health. The objective of this study is to assess the stress resilience of DR-PTB patients along with the factors associated with it.METHODS: A total of 385 adult DR-PTB patients with multidrug-resistant (MDR) and pre-extensive drug-resistant (pre-XDR) TB admitted to the National Institute of Diseases of the Chest Hospital (Dhaka, Bangladesh) between January 2020 and March 2021 were conveniently recruited. Resilience data were collected using a validated Stress Resilience Scale (RS 25) questionnaire.RESULTS: The mean resilience scores were significantly higher for patients with MDR-PTB than those with pre-XDR-PTB (P = 0.02). A majority of the MDR-PTB (77.0%) and pre-XDR-PTB (65.1%) patients belonged to the ≤45 years age group. Multiple linear regression revealed that sex (P < 0.001), level of education (P < 0.001), employment status (P = 0.003) and presence of asthma (P = 0.010) were significantly associated with stress resilience.CONCLUSION: We observed that stress resilience significantly differed between patients with MDR-PTB and those with pre-XDR-PTB based on sociodemographic characteristics.

DOI: 10.5588/ijtld.22.0648
PMID: 37353878 [Indexed for MEDLINE]

24. Molecular epidemiology and transmission dynamics of multi-drug resistant tuberculosis strains using whole genome sequencing in the Amhara region, Ethiopia.

BMC Genomics. 2023 Jul 17;24(1):400. doi: 10.1186/s12864-023-09502-2.

Shibabaw A(1)(2)(3)(4)(5), Gelaw B(6), Ghanem M(7), Legall N(8), Schooley AM(9), Soehnlen MK(9), Salvador LCM(10), Gebreyes W(#)(11)(12), Wang SH(#)(11)(13), Tessema B(#)(6).

BACKGROUND: Drug resistant Mycobacterium tuberculosis prevention and care is a major challenge in Ethiopia. The World health organization has designated Ethiopia as one of the 30 high burden multi-drug resistant tuberculosis (MDR-TB) countries. There is limited information regarding genetic diversity and transmission dynamics of MDR-TB in Ethiopia.
OBJECTIVE: To investigate the molecular epidemiology and transmission dynamics of MDR-TB strains using whole genome sequence (WGS) in the Amhara region.
METHODS: Forty-five MDR-TB clinical isolates from Amhara region were collected between 2016 and 2018, and characterized using WGS and 24-loci Mycobacterium Interspersed Repetitive Units Variable Number of Tandem Repeats (MIRU-VNTR) typing. Clusters were defined based on the maximum distance of 12 single nucleotide polymorphisms (SNPs) or alleles as the upper threshold of genomic relatedness. Five or less SNPs or alleles distance or identical 24-loci VNTR typing is denoted as surrogate marker for recent transmission.
RESULTS: Forty-one of the 45 isolates were analyzed by WGS and 44% (18/41) of the isolates were distributed into 4 clusters. Of the 41 MDR-TB isolates, 58.5% were classified as lineage 4, 36.5% lineage 3 and 5% lineage 1. Overall, TUR genotype (54%) was the predominant in MDR-TB strains. 41% (17/41) of the isolates were clustered into four WGS groups and the remaining isolates were unique strains. The predominant cluster (Cluster 1) was composed of nine isolates belonging to lineage 4 and of these, four isolates were in the recent transmission links.
CONCLUSIONS: Majority of MDR-TB strain cluster and predominance of TUR lineage in the Amhara region give rise to concerns for possible ongoing transmission. Efforts to strengthen TB laboratory to advance diagnosis, intensified active case finding, and expanded contact tracing activities are needed in order to improve rapid diagnosis and initiate early treatment. This would lead to the interruption of the transmission chain and stop the spread of MDR-TB in the Amhara region.

DOI: 10.1186/s12864-023-09502-2
PMCID: PMC10351181
PMID: 37460951 [Indexed for MEDLINE]

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

25. Comprehensive Drug Resistance Characterization of Pulmonary Tuberculosis in Algeria: Insights on Mycobacterium tuberculosis Strains by Whole-Genome Sequencing.

Microb Drug Resist. 2023 Jul;29(7):280-295. doi: 10.1089/mdr.2022.0321. Epub

2023 Apr 28.

Benremila D(1), Djoudi F(1), Gharout-Sait A(1), Kheloufi S(1), Spitaleri A(2), Battaglia S(2), Cabibbe AM(2), Cirillo DM(2).

In this study, we aimed to characterize drug-resistant strains by whole-genome sequencing (WGS), to describe the spreading lineages and the history of transmission. Drug susceptibility testing was performed by 96-well broth microdilution plates. The genomic DNA was extracted and purified; libraries were prepared and run on the Illumina NextSeq500 System. Among 82 isolates, 21 tuberculosis (TB) isolates (25.6%) were drug resistant, including 10 MDR and 4 pre-extensively drug-resistant (XDR)-TB. The mutation Ser315Thr in the katG gene was confirmed in 15 isolates. In rpoB, Ser450Leu and His445Asp mutations were the most common. Asp94Asn and Ala90Val mutations were reported in gyrA. The LAM family, the most TB drug resistant, was widely predominant in the north and the T sublineage in the south of the country. This study provides the first insight on TB drug resistance using WGS in Algeria and clearly describes the first pre-XDR-TB cases and lineage distribution across the country.

DOI: 10.1089/mdr.2022.0321
PMID: 37115530 [Indexed for MEDLINE]

26. Virtually screened novel sulfathiazole derivatives as a potential drug candidate for methicillin-resistant Staphylococcus aureus and multidrug-resistant tuberculosis.

10. J Biomol Struct Dyn. 2023 Jul;41(11):5086-5095. doi: 10.1080/07391102.2022.2079002. Epub 2022 May 28.

Nagendran S(1), Balasubramaniyan S(2), Irfan N(3).

Methicillin-resistant Staphylococcus aureus (MRSA) and multidrug-resistant tuberculosis (MDR-TB) is a leading cause of severe hospital and infection-related morbidity and mortality in the general population. There is a critical need for dynamic, powerful medication candidates to combat MRSA and MDR-TB infections in this specific setting. As a result, the current research focuses on the development of novel sulfathiazole derivative compounds that could be used as anti-MRSA and anti-MDR-TB agents. Virtual screening approaches were used to identify the potential lead sulfathiazole derivatives with the help of BIOVIA Discovery Studio 2017 software. In this in silico study, 10 novel sulfathiazole derivatives were virtually screened from 74 designed compounds. These 10 compounds had the best predictive docking scores in MRSA and MDR-TB receptors and were then put through a molecular dynamics simulation to explain protein stability, ligand characteristics and protein-ligand interactions. The

Lipinski rule and ADMET prediction results also suggested that 11 compounds (mol-12, mol-22, mol-23, mol-28, mol-30, mol-32, mol-34, mol-35, mol-45 and mol-47) have strong drug similarity features. Our findings imply that the 10 novel sulfathiazole compounds studied could be viable new therapeutic leads for MRSA and MDR-TB.

Plain Language Summary: Communicated by Ramaswamy H. Sarma.

DOI: 10.1080/07391102.2022.2079002
PMID: 35635120 [Indexed for MEDLINE]

27. Comparative Evaluation of GeneXpert MTB/RIF Ultra and GeneXpert MTB/RIF for Detecting Tuberculosis and Identifying Rifampicin Resistance in Pars Plana Vitrectomy Samples of Patients with Ocular Tuberculosis.

Ocul Immunol Inflamm. 2023 Jul;31(5):914-920. doi: 10.1080/09273948.2022.2064880. Epub 2022 Apr 20.

Sharma K(1), Sharma M(1)(2), Ayyadurai N(3), Dogra M(3), Sharma A(4), Gupta V(3), Singh R(3), Gupta A(3).

BACKGROUND: Xpert MTB/RIF Ultra (Ultra) was evaluated for the first time on Ocular tuberculosis (OTB) samples and compared with Xpert.
METHODS: Seventy five vitreous fluid samples (3 confirmed OTB, 47 clinically suspected OTB, and 25 controls) were subjected to Ultra, Xpert and Multiplex-PCR and compared against culture, composite reference standard (CRS), and gene sequencing.
RESULTS: The sensitivity of Ultra was 50% in diagnosing OTB (100% against culture and 46.8% against CRS). The overall sensitivity of Xpert and MPCR was 16% and 72%, respectively. Xpert missed three culture-positive cases and MPCR detected additional 11. Ultra and Xpert missed two and four cases of RifR, respectively. A total of 13(59%) cases were reported 'trace' by Ultra in which RifR could not be evaluated.
CONCLUSION: Ultra outperformed Xpert in diagnosing OTB. The advantage of Ultra's simultaneous RifR detection is lost since the trace bacterial loads in the specimens cause indeterminate results of RifR testing.Abbreviations: OTB: Ocular tuberculosis; Ultra: Xpert MTB/RIF Ultra; Xpert: Xpert MTB/RIF, MPCR: multiplex polymerase chain reaction; NAATs: Nucleic acid amplification tests; MLAMP: multitargeted loop-mediated isothermal amplification; PPV: positive predictive value; NPV: negative predictive value; EPTB: extrapulmonary tuberculosis; VF: vitreous fluid; DNA: deoxyribonucleic acid; ATT: antitubercular therapy; RifR: Rifampicin resistance; RifS: Rifampicin susceptible; RifI: Rifampicin indeterminate.

DOI: 10.1080/09273948.2022.2064880
PMID: 35442853 [Indexed for MEDLINE]

28. Host-pathogen relationship in retreated tuberculosis with major rifampicin resistance-conferring mutations.

Front Microbiol. 2023 Jul 4;14:1187390. doi: 10.3389/fmicb.2023.1187390. eCollection 2023.

Hang NTL(1), Hijikata M(2), Maeda S(3), Thuong PH(4), Huan HV(5), Hoang NP(6), Tam DB(7), Anh PT(8), Huyen NT(1)(9), Cuong VC(10), Kobayashi N(11), Wakabayashi K(2), Miyabayashi A(2), Seto S(2), Keicho N(12)(13).

INTRODUCTION: It is assumed that host defense systems eliminating the pathogen and regulating tissue damage make a strong impact on the outcome of tuberculosis (TB) disease and that these processes are affected by rifampicin (RIF) resistance-conferring mutations of Mycobacterium tuberculosis (Mtb). However, the host responses to the pathogen harboring different mutations have not been studied comprehensively in clinical settings. We analyzed clinico-epidemiological factors and blood transcriptomic signatures associated with major rpoB mutations conferring RIF resistance in a cohort study.
METHODS: Demographic data were collected from 295 active pulmonary TB patients with treatment history in Hanoi, Vietnam. When recruited, drug resistance-conferring mutations and lineage-specific variations were identified using whole-genome sequencing of clinical Mtb isolates. Before starting retreatment, total RNA was extracted from the whole blood of HIV-negative patients infected with Mtb that carried either the rpoB H445Y or rpoB S450L mutation, and the total RNA was subjected to RNA sequencing after age-gender matching. The individual RNA expression levels in the blood sample set were also measured using real-time RT-PCR. Logistic and linear regression models were used to assess possible associations.
RESULTS: In our cohort, rpoB S450L and rpoB H445Y were major RIF resistance-conferring mutations [32/87 (36.8%) and 15/87 (17.2%), respectively]. H445Y was enriched in the ancient Beijing genotype and was associated with nonsynonymous mutations of Rv1830 that has been reported to regulate antibiotic resilience. H445Y was also more frequently observed in genetically clustered strains and in samples from patients who had received more than one TB treatment episode. According to the RNA sequencing, gene sets involved in the interferon-γ and-α pathways were downregulated in H445Y compared with S450L. The qRT-PCR analysis also confirmed the low expression levels of interferon-inducible genes, including BATF2 and SERPING1, in the H445Y group, particularly in patients with extensive lesions on chest X-ray.
DISCUSSION: Our study results showed that rpoB mutations as well as Mtb sublineage with additional genetic variants may have significant effects on host

response. These findings strengthen the rationale for investigation of host-pathogen interactions to develop countermeasures against epidemics of drug-resistant TB.

DOI: 10.3389/fmicb.2023.1187390
PMCID: PMC10352910
PMID: 37469437

Conflict of interest statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

29. Structure-directed identification of pyridine-2-methylamine derivatives as MmpL3 inhibitors for use as antitubercular agents.

Eur J Med Chem. 2023 Jul 5;255:115351. doi: 10.1016/j.ejmech.2023.115351. Epub 2023 Apr 21.

Wen Y(1), Lun S(2), Jiao Y(1), Zhang W(1), Liu T(1), Yang F(3), Tang J(4), Bishai WR(5), Yu LF(6).

Mycobacterial membrane protein Large 3 (MmpL3), an inner membrane protein, plays a crucial role in the transport of mycolic acids that are essential for the viability of M. tuberculosis and has been a promising therapeutic target for new anti-TB agents. Herein, we report the discovery of pyridine-2-methylamine antitubercular compounds using a structure-based drug design strategy. Compound 62 stands out as the most potent compound with high activity against M. tb strain H37Rv (MIC = 0.016 μg/mL) as well as the clinically isolated strains of MDR/XDR-TB (MIC = 0.0039-0.0625 μg/mL), low Vero cell toxicity (IC50 ≥ 16 μg/mL), and moderate liver microsomal stability (CLint = 28 μL/min/mg). Furthermore, the resistant mutant of S288T due to single nucleotide polymorphism in mmpL3 was resistant to pyridine-2-methylamine 62, demonstrating compound 62 is likely target to MmpL3.

DOI: 10.1016/j.ejmech.2023.115351
PMCID: PMC10239758
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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.

30. Recurrent Tuberculosis Treatment Episodes in Children Presenting With Presumptive Pulmonary Tuberculosis in Cape Town, South Africa.

Pediatr Infect Dis J. 2023 Jul 1;42(7):543-548. doi: 10.1097/INF.0000000000003922. Epub 2023 Apr 19.

Mckenzie C(1), Schaaf HS(1), Croucamp R(1), Palmer M(1), Bosch C(1), Goussard P(1)(2), Rabie H(1)(2), Whitelaw A(3)(4), Hesseling AC(1), van Niekerk M(1), van der Zalm MM(1), Ghimenton-Walters E(1)(4).

BACKGROUND: Limited data are available on tuberculosis (TB) recurrence in children. The aim of this study was to explore the burden of and risk factors for recurrent TB treatment in children.
METHODS: A prospective, observational cohort study of children (0-13 years) presenting with presumptive pulmonary TB in Cape Town, South Africa from March 2012 to March 2017. Recurrent TB was defined as more than 1 episode of TB treatment (microbiologically confirmed and unconfirmed).
RESULTS: Of 620 children enrolled with presumptive pulmonary TB, data of 608 children were reviewed for TB recurrence after exclusions. The median age was 16.7 [interquartile range (IQR) 9.5-33.3] months, 324 (53.3%) were male and 72 (11.8%) children living with HIV (CLHIV). TB was diagnosed in 297 of 608 (48.8%), of whom 26 had previously received TB treatment, giving a prevalence of 8.8% recurrence: 22 (84.6%) had 1 and 4 (15.4%) had 2 prior TB treatment episodes. The median age of children with recurrent TB was 47.5 (IQR: 20.8-82.5) months at the current episode: 19 of 26 (73.1%) were CLHIV, of whom 12 of 19 (63.2%) were on antiretroviral therapy for a median 43.1 months and all 12 for longer than 6 months. None of the 9 children on antiretroviral treatment with available viral load (VL) data were virally suppressed (median VL, 22,983 copies/ml). Three of 26 (11.6%) children had documented microbiologically confirmed TB at 2 episodes. Four children (15.4%) received drug-resistant TB treatment at recurrence.
CONCLUSIONS: There was a high rate of recurrent treatment for TB in this cohort of young children, with CLHIV at the highest risk.

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PMID: 37204874 [Indexed for MEDLINE]

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

disclose.

31. Case Report: Ocular Tissue Diagnosis of Previously Undiagnosed, Extensively Drug-Resistant Pulmonary Tuberculosis.

Am J Trop Med Hyg. 2023 May 30;109(1):57-59. doi: 10.4269/ajtmh.22-0769. Print 2023 Jul 5.

Basu S(1), Murthy SI(1)(2), Mitra S(3), Chittiboyina S(4), Shanmugham S(5).

We describe a patient with concurrent ocular and pulmonary tuberculosis (TB) in whom the diagnosis of extensively drug-resistant TB was made through phenotypic drug-sensitivity testing of an ocular fluid sample after sputum testing yielded incomplete results. Our results are remarkable, because culture-based diagnosis of TB in ocular fluid is unusual. We not only overcame this limitation, but also were able to create a complete drug-sensitivity testing profile from ocular samples, which led to effecting appropriate therapy for the patient.

DOI: 10.4269/ajtmh.22-0769
PMCID: PMC10324008
PMID: 37253441 [Indexed for MEDLINE]

32. Children´s priorities to improve the acceptability of MDR-TB treatment: qualitative data from South Africa.

Int J Tuberc Lung Dis. 2023 Jul 1;27(7):543-550. doi: 10.5588/ijtld.22.0573.

Wademan DT(1), Viljoen L(1), Jacobs S(1), Meyerson K(1), Nombewu Y(1), Busakwe L(1), Schaaf HS(1), Hesseling AC(1), Winckler J(1), Garcia-Prats AJ(2), Hoddinott G(1).

BACKGROUND: Multidrug-resistant TB (MDR-TB) treatment for children frequently includes unpalatable drugs with low overall acceptability. This can negatively impact children and their caregivers´ treatment experiences and is an important contributor to poor adherence, and potentially, poor treatment outcomes. Children and their caregivers´ preferences for MDR-TB treatment are not well documented. We describe children and caregivers´ priorities to inform future MDR-TB treatment regimens.METHODS: We conducted a cross-sectional qualitative study at a TB hospital in South Africa using semi-structured interviews and participatory research activities with caregivers and children routinely diagnosed and treated for MDR-TB between June and August 2018.RESULTS: We conducted 15 interviews with children and their caregivers. Children ranged from 2 to 17 years of age (median age: 8.3 years). Children and caregivers had an overall negative experience of MDR-TB treatment. Children and caregivers

described how future MDR-TB drugs and regimens should prioritise sweeter flavours, fewer pills, brighter colours, and formulations that are easy to prepare and administer and dispensed in colourful, small and discrete packaging.CONCLUSIONS: MDR-TB treatment acceptability remains low, and negatively impacts children and their caregivers´ treatment experiences. Improving the overall acceptability of MDR-TB treatment requires engaging with children and their caregivers to better understand their priorities for new treatment regimens and child-friendly formulations.

DOI: 10.5588/ijtld.22.0573
PMID: 37353869 [Indexed for MEDLINE]

33. Children deserve simple, short, safe, and effective treatment for rifampicin-resistant tuberculosis.

Lancet Infect Dis. 2023 Jul;23(7):778-780. doi: 10.1016/S1473-3099(23)00349-3. Epub 2023 May 25.

Garcia-Prats AJ(1), Hoddinott G(2), Howell P(3), Hughes J(2), Jean-Philippe P(4), Kim S(5), Palmer M(2), Schaaf HS(2), Seddon JA(6), Svensson E(7), Hesseling AC(2).

DOI: 10.1016/S1473-3099(23)00349-3
PMID: 37245523 [Indexed for MEDLINE]

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34. Cisatracurium besylate rescues Mycobacterium Tuberculosis-infected macrophages

from necroptosis and enhances the bactericidal effect of isoniazid.

Int Immunopharmacol. 2023 Jul;120:110291. doi: 10.1016/j.intimp.2023.110291. Epub 2023 May 12.

Wen Q(1), Zhang J(1), Zhang Z(1), Chen L(1), Liu H(1), Han Z(1), Chen Y(1), Wang K(1), Liu J(1), Sai N(1), Zhou X(1), Zhou C(1), Hu S(1), Ma L(2).

OBJECTIVE: Tuberculosis is the leading killer among the chronic single-source infectious diseases. Mycobacterium tuberculosis can induce necrotic-dominant multiple modes of cell death in macrophages, which accelerates bacterium dissemination and expands tissue injury in host lungs. Mining drugs to counteract Mycobacterium tuberculosis-induced cell death would be beneficial to tuberculosis patients.
METHODS: In this study, the protective drug was screened out from the FDA-approved drug library in Mycobacterium tuberculosis-infected macrophages with CCK-8 assay. The death mode regulated by the drug was identified using transcriptomic sequencing, cytomorphological observation, and in the experimental mouse Mycobacterium tuberculosis-infection model. The functional mechanism was explored using western blot, co-immunoprecipitation, and DARTS assay. The intracellular bacterial survival was detected using colony forming unit assays.
RESULTS: Cisatracurium besylate was identified to be highly protective for the viability of macrophages during Mycobacterium tuberculosis infection via inhibiting necroptosis. Cisatracurium besylate prevented RIPK3 to be associated with the executive molecule MLKL for forming the necroptotic complex, resulting in the inhibition of MLKL phosphorylation and pore formation on cell membrane. However, Cisatracurium besylate did not interfere with the association between RIPK3 with its upstream kinase RIPK1 or ZBP1 but regulated RIPK3 autophosphorylation. Moreover, Cisatracurium besylate significantly inhibited the expansion of intracellular Mycobacterium tuberculosis both in vitro and in vivo, which also displayed a strong auxiliary bacteriostatic effect to support the therapeutic efficacy of isoniazid and rifampicin, the first-line anti-tubercular drugs.
CONCLUSION: Cisatracurium besylate performs anti-Mycobacterium tuberculosis and anti-necroptotic roles, which potentiates its application to be an adjuvant drug for antituberculosis therapy to assist the battle against drug-resistant tuberculosis.

DOI: 10.1016/j.intimp.2023.110291
PMID: 37182451 [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.

35. Characterization of Two Novel Inhibitors of the Mycobacterium tuberculosis Cytochrome bc(1) Complex.

Antimicrob Agents Chemother. 2023 Jul 18;67(7):e0025123. doi: 10.1128/aac.00251-23. Epub 2023 Jun 26.

Gries R(#)(1)(2)(3), Dal Molin M(#)(1)(2), Chhen J(#)(1)(2), van Gumpel E(1)(2), Dreyer V(4)(5), Niemann S(4)(5), Rybniker J(1)(2)(3).

Drug-resistant tuberculosis is a global health care threat calling for novel effective treatment options. Here, we report on two novel cytochrome bc1 inhibitors (MJ-22 and B6) targeting the Mycobacterium tuberculosis respiratory chain with excellent intracellular activities in human macrophages. Both hit compounds revealed very low mutation frequencies and distinct cross-resistance patterns with other advanced cytochrome bc1 inhibitors.

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PMCID: PMC10353358
PMID: 37358461 [Indexed for MEDLINE]

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

36. Detection of antigen Ag85B expression is useful for the diagnosis of tuberculosis, especially for those with an antituberculosis treatment history.

Am J Clin Pathol. 2023 Jul 5;160(1):62-71. doi: 10.1093/ajcp/aqad012.

Dong Y(1), Zhou L(1), Zhang C(1), Li K(1), Liu Z(1), Chen X(1), Che N(1).

OBJECTIVES: The present study used immunohistochemistry (IHC) to detect antigen Ag85B in tissue sections and aimed to evaluate its validity in histopathologic diagnosis of tuberculosis (TB).
METHODS: In total, 204 patients with confirmed TB and 40 other diseases were included in the present study. Ziehl-Neelsen (Z-N) stains, IHC (anti-Ag85B), and quantitative fluorescence polymerase chain reaction were used to detect acid-fast bacilli, Mycobacterium tuberculosis (MTB) antigen, and MTB DNA.
RESULTS: Immunohistochemistry was significantly more sensitive than Z-N stains (93.1% vs 67.2%; P < .001). The sensitivity of Z-N stains significantly correlated with anti-TB treatment history. The sensitivity of Z-N stains was

lower in rifampicin (RIF)-resistant TB compared with RIF-sensitive TB (52.8% vs 69.0%; P = .091) and those without treatment history (52.8% vs 84.0%; P = .015). However, IHC was not significantly affected by treatment history (P = .410). Moreover, expression patterns of Ag85B were dependent on treatment history and commonly showed weak scattered spots in RIF-susceptible TB. Conversely, strong brown rods were often found in those with RIF-resistant TB.
CONCLUSIONS: Immunohistochemistry is a simple, sensitive technique for the diagnosis of TB, especially for those patients with treatment history. The expression pattern of Ag85B is a potential marker for evaluating anti-TB treatment response.

DOI: 10.1093/ajcp/aqad012
PMID: 36943303 [Indexed for MEDLINE]

37. Molecular dynamic assisted investigation on impact of mutations in deazaflavin dependent nitroreductase against pretomanid: a computational study.

J Biomol Struct Dyn. 2023 Jul;41(10):4421-4443. doi: 10.1080/07391102.2022.2069156. Epub 2022 May 14.

Singh R(1), Shaheer M(1), Sobhia ME(1).

In the past decade, TB drugs belonging to the nitroimidazole class, pretomanid and delamanid, have been authorised to treat MDR-TB and XDR-TB. With a novel inhibition mechanism and a reduction in the span of treatment, it is now being administered in various combinations. This approach is not the ultimate remedy since the target protein Deazaflavin dependent nitroreductase (Ddn) has a high mutation frequency, and already pretomanid resistant clinical isolates are reported in various studies. Ddn is essential for M.tuberculosis to emerge from hypoxia, and point mutations in critical residues confer resistance to Nitro-imidazoles. Among the pool of available mutants, we have selected seven mutants viz DdnL49P, DdnY65S, DdnS78Y, DdnK79Q, DdnW88R, DdnY133C, and DdnY136S, all of which exhibited resistance to pretomanid. To address this issue, through computational study primarily by MD simulation, we attempted to elucidate these point mutations' impact and investigate the resistance mechanism. Hence, the DdnWT and mutant (MT) complexes were subjected to all-atom molecular dynamics (MD) simulations for 100 ns. Interestingly, we observed the escalation of the distance between cofactor and ligand in some mutants, along with a significant change in ligand conformation relative to the DdnWT. Moreover, we confirmed that mutations rendered ligand instability and were ejected from the binding pocket

as a result. In conclusion, the results obtained provide a new structural insight and vital clues for designing novel inhibitors to combat nitroimidazole resistanceCommunicated by Ramaswamy H. Sarma.

DOI: 10.1080/07391102.2022.2069156
PMID: 35574601 [Indexed for MEDLINE]

38. Making the Case for All-Oral, Shorter Regimens for Children with Drug-Resistant Tuberculosis.

Am J Respir Crit Care Med. 2023 Jul 15;208(2):130-131. doi: 10.1164/rccm.202304-0670VP.

Patankar S(1), Cruz AT(2), Douglas-Jones B(3), Garcia-Prats A(3)(4), Kay A(2), Reuter A(5), Schaaf HS(3), Seddon JA(3)(6), Sharma S(7), Starke J(2), Tommasi M(8), Triasih R(9), Furin JJ(10).

DOI: 10.1164/rccm.202304-0670VP
PMID: 37276531 [Indexed for MEDLINE]

39. A tale of two inhibitors: diarylquinolines and squaramides.

EMBO J. 2023 Jul 12:e114912. doi: 10.15252/embj.2023114912. Online ahead of print.

Chen J(1)(2), Ekiert DC(1)(2).

The diarylquinoline bedaquiline (BDQ) is an FDA-approved drug for the treatment of multidrug-resistant tuberculosis that targets the mycobacterial adenosine triphosphate (ATP) synthase, a key enzyme in cellular respiration. In a recent study, Courbon et al (2023) examine the interaction between Mycobacterium smegmatis ATP synthase with the second generation diarylquinoline TBAJ-876 and the squaramide inhibitor SQ31f, showing that both drugs prevent the rotatory motions needed for enzymatic function.

DOI: 10.15252/embj.2023114912
PMID: 37435707

40. Pattern of InhA and KatG mutations in isoniazid mono resistant Mycobacterium tuberculosis isolates from Odisha.

Indian J Med Microbiol. 2023 Jul-Aug;44:100373. doi:

10.1016/j.ijmmb.2023.100373. Epub 2023 May 11.

Kumar S(1), Rout SS(1), Kar S(1), Bal HB(1), Turuk J(2), Das D(2), Hota PK(3), Pati S(2), Giri S(4).

We conducted a retrospective analysis of the line probe assay (LPA) data during January to December 2019, from 8 districts of Odisha. The prevalence of Hr-TB (isoniazid resistance only) was 1.53% (50/3272) with a range of 0-3.4% in the 8 districts. Of the 50 Hr-TB strains, katG mutation and inhA mutations were seen in 74% (37/50) and 26% (13/50) strains respectively. S315T1 and C15T were common mutations in katG and inhA respectively. Since these mutations are closely related to high- or low degree resistance to INH, it has therapeutic implications.

DOI: 10.1016/j.ijmmb.2023.100373
PMID: 37356845 [Indexed for MEDLINE]

Conflict of interest statement: Declaration of competing interest None.

41. [Evaluation of the performance of InnowaveDX MTB/RIF for the detection of Mycobacterium tuberculosis complex and rifampicin resistance].

Zhonghua Jie He He Hu Xi Za Zhi. 2023 Jul 12;46(7):658-663. doi: 10.3760/cma.j.cn112147-20221104-00877.

Wang YP(1), Tan YH(2), Li X(3), Wang J(2), Chen CG(3), Xu J(4), Xiang J(4).

Objective: To evaluate the performance of Mycobacterium tuberculosis and rifampicin resistance mutation detection kit (InnowaveDX MTB/RIF, referred to as "InnowaveDX") in diagnosing tuberculosis and rifampicin resistance using sputum samples. Methods: From June 19, 2020 to May 16, 2022, patients with suspected tuberculosis were prospectively and consecutively enrolled in Hunan Provincial Tuberculosis Prevention and Control Institute, Henan Provincial Hospital of Infectious Diseases and Wuhan Jinyintan Hospital. A total of 1 328 patients with suspected tuberculosis were finally included. According to the inclusion and exclusion criteria, 1 035 pulmonary tuberculosis patients (357 were confirmed tuberculosis cases and 678 were clinically diagnosed tuberculosis cases) and 180 non-tuberculosis patients were finally included. Sputum samples were collected from all patients for routine sputum smear acid-fastness tests, mycobacterial culture and drug susceptibility testing. Moreover, the diagnostic value of Xpert®MTB/RIF (referred to as "Xpert") and InnowaveDXin detecting tuberculosis

and rifampicin resistance was evaluated. Clinical diagnosis and culture results of Mycobacterium tuberculosis were used as reference standards to assess tuberculosis diagnosis, and phenotypic drug sensitivity and Xpert were used as reference standards to assess rifampicin resistance. The sensitivity, specificity, positive predictive value and negative predictive value of the two methods for tuberculosis diagnosis and rifampicin resistance were analyzed. The consistency of the two techniques was analyzed usingkappa test. Results: Taking clinical diagnosis as the reference standard, the detection sensitivity of InnowaveDX [58.0% (600/1 035)] was higher than that of Xpert [51.7% (535/1 035)] in 1035 patients with pulmonary tuberculosis, and the difference was statistically significant (P<0.001). In 270 pulmonary tuberculosis patients with culture-positive pulmonary tuberculosis identified as M.tuberculosis-complex, the positive rates of InnowaveDX and Xpert were both high [99.6%(269/270)and 98.2%(265/270), respectively] and there was no statistical difference. In culture-negative patients with pulmonary tuberculosis, the sensitivity of InnowaveDX was 38.8% (198/511), which was higher than that of Xpert (29.4%, 150/511), and the difference was statistically significant (P<0.001). Taking phenotypic drug-susceptibility testing (DST) as reference, the sensitivity of InnowaveDX to rifampicin resistance was 99.0% (95%CI: 94.7%-100.0%) and the specificity was 94.0%(95%CI: 88.5%-97.4%). With Xpert as the reference, the sensitivity and specificity of InnowaveDX were 97.1% (95%CI: 93.4%-99.1%) and 99.7% (95%CI: 98.4%-100.0%), respectively, and the kappa value was 0.97 (P<0.001). Conclusions: InnowaveDX show a high sensitivity for detecting Mycobacterium tuberculosis, especially in pulmonary tuberculosis patients with a clinical diagnosis and negative culture results. It also showed high sensitivity in detecting rifampicin resistance with DST and Xpert as reference respectively. InnowaveDX is an early and accurate diagnostic tool for TB and drug-resistant TB, particularly suitable for application in low- and middle-income countries.

DOI: 10.3760/cma.j.cn112147-20221104-00877
PMID: 37402655 [Indexed for MEDLINE]

42. Cell wall and immune modulation by Rv1800 (PPE28) helps M. smegmatis to evade intracellular killing.

Int J Biol Macromol. 2023 Jul 14:125837. doi: 10.1016/j.ijbiomac.2023.125837. Online ahead of print.

Anand PK(1), Saini V(2), Kaur J(3), Kumar A(1), Kaur J(4).

Rv1800 is predicted as PPE family protein found in pathogenic mycobacteria only. Under acidic stress, the rv1800 gene was expressed in M. tuberculosis H37Ra. In-silico study showed lipase/esterase activity in C-terminus PE-PPE domain having pentapeptide motif with catalytic Ser-Asp-His residue. Full-length Rv1800

and C-terminus PE-PPE domain proteins showed esterase activity with pNP-C4 at the optimum temperature of 40 °C and pH 8.0. However, the N-terminus PPE domain showed no esterase activity, but involved in thermostability of Rv1800 full-length protein. M. smegmatis expressing rv1800 (MS_Rv1800) showed altered colony morphology and a significant resistance to numerous environmental stresses, antibiotics and higher lipid content. In extracellular and membrane fraction, Rv1800 protein was detected, while C terminus PE-PPE was present in cytoplasm, suggesting the role of N-terminus PPE domain in transportation of protein. MS_Rv1800 infected macrophage showed higher intracellular survival and low production of ROS, NO and expression levels of iNOS and pro-inflammatory cytokines, while induced expression of the anti-inflammatory cytokines. The Rv1800, PPE and PE-PPE showed antibody-mediated immunity in MDR-TB and PTB patients. Overall, these results confirmed the esterase activity in the C-terminus and function of N-terminus in thermostabilization and transportation; predicting the role of Rv1800 in immune/lipid modulation to support intracellular mycobacterium survival.

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PMID: 37455004

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