Pub Med Open Access

1. Economic burden of multidrug-resistant tuberculosis on patients and households: a global systematic review and meta-analysis.

Sci Rep. 2023 Dec 15;13(1):22361. doi: 10.1038/s41598-023-47094-9.

Akalu TY(1)(2)(3), Clements ACA(4)(5), Wolde HF(6)(4)(7), Alene KA(6)(4).

Multidrug-resistant tuberculosis (MDR-TB) is a major health threat worldwide, causing a significant economic burden to patients and their families. Due to the longer duration of treatment and expensive second-line medicine, the economic burden of MDR-TB is assumed to be higher than drug-susceptible TB. However, the costs associated with MDR-TB are yet to be comprehensively quantified. We conducted this systematic review and meta-analysis to determine the global burden of catastrophic costs associated with MDR-TB on patients and their households. We systematically searched five databases (CINHAL, MEDLINE, Embase, Scopus, and Web of Science) from inception to 2 September 2022 for studies reporting catastrophic costs on patients and affected families of MDR-TB. The primary outcome of our study was the proportion of patients and households with catastrophic costs. Costs were considered catastrophic when a patient spends 20% or more of their annual household income on their MDR-TB diagnosis and care. The pooled proportion of catastrophic cost was determined using a random-effects meta-analysis. Publication bias was assessed using visualization of the funnel plots and the Egger regression test. Heterogeneity was assessed using I2, and sub-group analysis was conducted using study covariates as stratification variables. Finally, we used the Preferred Reporting Items for Reporting Systematic Review and Meta-Analysis-20 (PRISMA-20). The research protocol was registered in PROSPERO (CRD42021250909). Our search identified 6635 studies, of which 11 were included after the screening. MDR-TB patients incurred total costs ranging from $USD 650 to $USD 8266 during treatment. The mean direct cost and indirect cost incurred by MDR-TB patients were $USD 1936.25 (SD ± $USD 1897.03) and $USD 1200.35 (SD ± $USD 489.76), respectively. The overall burden of catastrophic cost among MDR-TB patients and households was 81.58% (95% Confidence Interval (CI) 74.13-89.04%). The catastrophic costs incurred by MDR-TB patients were significantly higher than previously reported for DS-TB patients. MDR-TB patients incurred more expenditure for direct costs than indirect costs. Social protection and financial support for patients and affected families are needed to mitigate the catastrophic economic consequences of MDR-TB.

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PMCID: PMC10724290
PMID: 38102144 [Indexed for MEDLINE]

2. Optimizing dosing of the cycloserine pro-drug terizidone in children with rifampicin-resistant tuberculosis.

Antimicrob Agents Chemother. 2023 Dec 14;67(12):e0061123. doi: 10.1128/aac.00611-23. Epub 2023 Nov 16.

van der Laan LE(1)(2), Garcia-Prats AJ(2)(3), McIlleron H(1), Abdelwahab MT(1), Winckler JL(2), Draper HR(2), Wiesner L(1), Schaaf HS(2), Hesseling AC(2), Denti P(1).

There are no pharmacokinetic data in children on terizidone, a pro-drug of cycloserine and a World Health Organization (WHO)-recommended group B drug for rifampicin-resistant tuberculosis (RR-TB) treatment. We collected pharmacokinetic data in children <15 years routinely receiving 15-20 mg/kg of daily terizidone for RR-TB treatment. We developed a population pharmacokinetic model of cycloserine assuming a 2-to-1 molecular ratio between terizidone and cycloserine. We included 107 children with median (interquartile range) age and weight of 3.33 (1.55, 5.07) years and 13.0 (10.1, 17.0) kg, respectively. The pharmacokinetics of cycloserine was described with a one-compartment model with first-order elimination and parallel transit compartment absorption. Allometric scaling using fat-free mass best accounted for the effect of body size, and clearance displayed maturation with age. The clearance in a typical 13 kg child was estimated at 0.474 L/h. The mean absorption transit time when capsules were opened and administered as powder was significantly faster compared to when capsules were swallowed whole (10.1 vs 72.6 min) but with no effect on bioavailability. Lower bioavailability (-16%) was observed in children with weight-for-age z-score below -2. Compared to adults given 500 mg daily terizidone, 2022 WHO-recommended pediatric doses result in lower exposures in weight bands 3-10 kg and 36-46 kg. We developed a population pharmacokinetic model in children for cycloserine dosed as terizidone and characterized the effects of body size, age, formulation manipulation, and underweight-for-age. With current terizidone dosing, pediatric cycloserine exposures are lower than adult values for several weight groups. New optimized dosing is suggested for prospective evaluation.

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PMCID: PMC10720412
PMID: 37971239 [Indexed for MEDLINE]

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

3. Treatment of drug-resistant tuberculosis in children and young adolescents in Brazil.

J Clin Tuberc Other Mycobact Dis. 2023 Aug 2;33:100388. doi: 10.1016/j.jctube.2023.100388. eCollection 2023 Dec.

Bruzadelli Paulino da Costa F(1), Zamboni Berra T(1), Garcia de Almeida Ballestero J(1), Bartholomay Oliveira P(2), Maria Pelissari D(3), Mathias Alves Y(1), Carlos Vieira Ramos A(1), Queiroz Rocha de Paiva J(4), Kehinde Ayandeyi

Teibo T(1), Alexandre Arcêncio R(1).

INTRODUCTION: Drug-resistant tuberculosis (DR-TB) is a global threat and a challenge for public health authorities worldwide. In children, the diagnosis is even more challenging and DR-TB is poorly described in the literature, as are its treatment outcomes. In this study, we aimed to describe the treatment of drug-resistant TB in children and young adolescents in Brazil.

METHODS: A descriptive epidemiological study of treatment for DR-TB in children under 15 years of age in Brazil between 2013 and 2020. The primary data source was the Information System for Special Tuberculosis Treatments (SITE-TB). Categorical variables were analyzed using relative frequencies (%) and continuous variables by measures of central tendency to characterize the profile of the cases, namely: sociodemographic, clinical characteristics, procedures, tests performed and treatment success. In order to verify the distribution of cases, a spatial analysis was carried out based on the municipality where the cases resided.

RESULTS: Between 2013 and 2020, 19,757 tuberculosis (TB) cases occurred in children aged <15 years in Brazil, and 46 cases of treatment for DR-TB were reported during the same period (annual average of 6 cases). Of these, 73.9% were aged 10-14, 65.2% were male, 4.3% were HIV+ and 43.3% were underweight (BMI<18.5) at the start of treatment. 17.4% had previous contact with TB, 69.6% had primary resistance, 47.8% multidrug resistance. The median duration of treatment was 15 months. DOT and standardized treatment regimen were performed in 52.2% of cases. Bacilloscopy was performed for 97.8% (57.8% positive); culture for 89.1% (75.6% positive), rapid molecular test for 73.9% with proven resistance to rifampicin in 55.8%. Susceptibility testing revealed resistance mainly to isoniazid (87.8%) and rifampicin (60.6%). 73.9% of cases were successfully treated and one death was reported. Cases were treated in 26 Brazilian municipalities, with the majority in Rio de Janeiro (15) and São Paulo (4).

CONCLUSION: DR-TB treatment was recorded in <1% of general TB cases in children and young adolescents, suggesting underreporting of drug-resistant cases in the country. Despite the low number of registered cases, the data reflect the situation of DR-TB in this population and describe important aspects of the problem, as the child needs comprehensive, individualized care, with support from different professionals. We recommend a strengthening of the country's referral services for the care of children with DR-TB so that surveillance and health care services can work together to identify and follow up cases.

DOI: 10.1016/j.jctube.2023.100388

PMCID: PMC10425933
PMID: 37588725

4. Strain structure analysis of Mycobacterium tuberculosis circulating among HIV negative, positive and drug resistant TB patients attending chest clinics in Western Kenya.

BMC Pulm Med. 2023 Dec 9;23(1):497. doi: 10.1186/s12890-023-02802-z.

Ogwang MO(1), Diero L(2), Ng'ong'a F(3), Magoma G(3), Mutharia L(4), Imbuga M(3), Ngugi C(3).

BACKGROUND: Despite global tuberculosis (TB) interventions, the disease remains one of the major public health concerns. Kenya is ranked 15th among 22 high burden TB countries globally.

METHODS: A cross-sectional study was conducted in Western Kenya, which comprises 10 counties. A multistage sampling method was used where a single sub-county was randomly selected followed by sampling two high volume health facility from each sub-county. Identification of spoligotype profiles and their family distribution and lineage level were achieved by comparison with SITVIT database.
RESULTS: Lineage distribution pattern revealed that the most predominant lineage was CAS 220 (39.8%) followed by Beijing 128 (23.1%). The other lineages identified were T, LAM, H, X, S and MANU which were quantified as 87 (15.7%), 67 (12.1%), 16 (2.8%), 10 (1.8%), 8 (1.4%) and 5 (0.9%) respectively. CAS and Beijing strains were the most predominant lineage in both HIV negative and positive TB patients. The Beijing lineage was also the most predominant in resistant M. tuberculosis strains as compared to wild type. A total of 12 (2.0%) were orphaned M. tuberculosis strains which were spread across all the 10 counties of the study site. In multivariate logistic regression adjusting for potential cofounders three potential risk factors were significant. HIV status (OR = 1.52, CI = 0.29-3.68 and P value of 0.001), Alcohol use (OR = 0.59, CI = 0.43-3.12 and P-value =0.001) and cross border travel (OR = 0.61, CI = 0.49-3.87 and P value = 0.026). Most M. tuberculosis clinical isolates showed genetic clustering with multivariate logistic regression indicating three potential risk factors to clustering. HIV status (OR = 1.52, CI = 0.29-3.68 and P value of 0.001), Alcohol use (OR = 0.59, CI = 0.43-3.12 and P-value =0.001) and cross border travel (OR = 0.61, CI = 0.49-3.87 and P value = 0.026).
CONCLUSION: There exist diverse strains of M. tuberculosis across the 10 counties of Western Kenya. Predominant distribution of clustered genotype points to the fact that most TB cases in this region are as a result of resent transmission other than activation of latent TB.

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PMCID: PMC10709907
PMID: 38071287 [Indexed for MEDLINE]

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

5. Drug-Resistant Tuberculosis and COVID-19: A Scoping Review on a New Threat to Antimicrobial Resistance.

Rev Bras Enferm. 2023 Dec 4;76Suppl 1(Suppl 1):e20220803. doi: 10.1590/0034-7167-2022-0803. eCollection 2023.

Silva BPMD(1), Almeida AS(1), Sérgio MGM(1), Gatto TC(1), Carasek VP(1), Yamamura M(1).

OBJECTIVE: To assess the impact of COVID-19 on the morbidity and mortality associated with drug-resistant tuberculosis (DR-TB).

METHODS: A comprehensive review of articles published in international databases since December 2019 was conducted. The findings are presented in a narrative format, supplemented with tables, diagrams, and a map created using ArcGIS software.

RESULTS: Thirty-five studies were selected, highlighting the significant consequences of COVID-19 on TB and DR-TB treatment progress. Four main thematic areas were identified: Clinical and epidemiological aspects of the interaction between COVID-19 and DR-TB; Management of physical resources and the team; Challenges and circumstances; Perspectives and possibilities.

CONCLUSIONS: This study revealed that the COVID-19 pandemic significantly negatively impacted the control of long-standing diseases like TB, particularly in the context of morbidity and mortality related to DR-TB.

DOI: 10.1590/0034-7167-2022-0803
PMCID: PMC10695069
PMID: 38055430 [Indexed for MEDLINE]

6. Clinical features, resistance patterns and treatment outcomes of drug-resistant extra-pulmonary tuberculosis: A scoping review.

J Clin Tuberc Other Mycobact Dis. 2023 Aug 4;33:100390. doi: 10.1016/j.jctube.2023.100390. eCollection 2023 Dec.

Miiro E(1), Olum R(2), Baluku JB(3)(4).

BACKGROUND: Drug-resistant tuberculosis (DR-TB) is a threat to tuberculosis (TB) control. Extra-pulmonary forms of DR-TB (DR-epTB) are not well characterized. This review summarizes the clinical features, resistance patterns and treatment outcomes of DR-epTB.

METHODS: We searched EMBASE to identify studies that reported drug-resistance among extra-pulmonary TB sites. All age groups were included in this review. Studies which did not describe drug-resistance patterns at extra-pulmonary TB sites were excluded. We summarized the proportion of resistance to individual anti-TB drugs as well as multi-drug resistant (MDR), pre-extensively drug resistant (pre-XDR) and extensively drug-resistant (XDR) TB.

RESULTS: Eighteen studies with a total of 10,222 patients with extra-pulmonary TB of whom 1,236 (12.0%) had DR-epTB, were included in this review. DR-epTB was mostly reported in young people aged 28 to 46 years. While TB meningitis is the most commonly studied form, adenitis is the commonest form of DR-epTB reported in 21% to 47%. Central nervous system TB (3.8% to 51.6%), pleural TB (11.3% to 25.9%), skeletal TB (9.4% to 18.1%), abdominal TB (4.3% to 6.5%), and disseminated TB (3.8%) are also encountered. The HIV co-infection rate is reported to be 5.0% to 81.3% while 2.6% to 25.4 % have diabetes mellitus. Clinical symptoms of DR-epTB are consistent with morbidity in the affected body system. Among patients with DR-epTB, the proportion of MDR TB was 5% to 53% while that for pre-XDR TB and XDR TB was 3% to 40% and 4% to 33%, respectively. Treatment success is achieved in 26% to 83% of patients with DR-epTB while death, treatment loss-to-follow up, and treatment failure occur in 2% to 76%, 7% to 15%, and 0% to 4% respectively. Patients with DR-epTB were reported to have poorer outcomes than those with pulmonary DR-TB and extra-pulmonary drug-susceptible TB.

CONCLUSION: Clinical features of DR-epTB are similar to those observed among people with drug-susceptible EPTB but patients with DR-epTB post worse treatment outcomes.

DOI: 10.1016/j.jctube.2023.100390
PMCID: PMC10425399
PMID: 37588726

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.

7. Mycobacteriophage D29 Lysin B exhibits promising anti-mycobacterial activity against drug-resistant Mycobacterium tuberculosis.

Microbiol Spectr. 2023 Dec 12;11(6):e0459722. doi: 10.1128/spectrum.04597-22. Epub 2023 Oct 6.

Singh AK(1), Gangakhedkar R(2), Thakur HS(1), Raman SK(3), Patil SA(1), Jain V(2).

To combat the rapidly emerging drug-resistant M. tuberculosis, it is now essential to look for alternative therapeutics. Mycobacteriophages can be considered as efficient therapeutics due to their natural ability to infect and kill mycobacteria including M. tuberculosis. Here, we have exploited the mycolyl-arabinogalactan esterase property of LysB encoded from mycobacteriophage D29. This study is novel in terms of targeting a multi-drug-resistant pathogenic strain of M. tuberculosis with LysB and also examining the combination of anti-TB drugs and LysB. All the experiments include external administration of LysB. Therefore, the remarkable lytic activity of LysB overcomes the difficulty to enter the complex cell envelope of mycobacteria. Targeting the intracellularly located M. tuberculosis by LysB and non-toxicity to macrophages take the process of the development of LysB as a drug one step ahead, and also, the interaction studies with rifampicin and isoniazid will help to form a new treatment regimen against tuberculosis.

DOI: 10.1128/spectrum.04597-22
PMCID: PMC10714809
PMID: 37800970 [Indexed for MEDLINE]

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

8. mHealth application for improving treatment outcomes for patients with multidrug-resistant tuberculosis in Vietnam: an economic evaluation protocol for the V-SMART trial.

BMJ Open. 2023 Dec 11;13(12):e076778. doi: 10.1136/bmjopen-2023-076778.

Cheng Q(#)(1), Dang T(#)(2), Nguyen TA(2)(3), Velen K(3), Nguyen VN(4), Nguyen BH(4), Vu DH(5), Long CH(2), Do TT(4), Vu TM(6), Marks GB(2)(7), Yapa M(3), Fox GJ(2)(3), Wiseman V(8)(9).

INTRODUCTION: The Strengthen the Management of Multidrug-Resistant Tuberculosis

in Vietnam (V-SMART) trial is a randomised controlled trial of using mobile health (mHealth) technologies to improve adherence to medications and management of adverse events (AEs) in people with multidrug-resistant tuberculosis (MDR-TB) undergoing treatment in Vietnam. This economic evaluation seeks to quantify the cost-effectiveness of this mHealth intervention from a healthcare provider and societal perspective.

METHODS AND ANALYSIS: The V-SMART trial will recruit 902 patients treated for MDR-TB across seven participating provinces in Vietnam. Participants in both intervention and control groups will receive standard community-based therapy for MDR-TB. Participants in the intervention group will also have a purpose-designed App installed on their smartphones to report AEs to health workers and to facilitate timely management of AEs. This economic evaluation will compare the costs and health outcomes between the intervention group (mHealth) and the control group (standard of care). Costs associated with delivering the intervention and health service utilisation will be recorded, as well as patient out-of-pocket costs. The health-related quality of life (HRQoL) of study participants will be captured using the 36-Item Short Form Survey (SF-36) questionnaire and used to calculate quality-adjusted life-years (QALYs). Incremental cost-effectiveness ratios (ICERs) will be based on the primary outcome (proportion of patients with treatment success after 24 months) and QALYs gained. Sensitivity analysis will be conducted to test the robustness of the ICERs. A budget impact analysis will be conducted from a payer perspective to provide an estimate of the total budget required to scale-up delivery of the intervention.

ETHICS AND DISSEMINATION: Ethical approval for the study was granted by the University of Sydney Human Research Ethics Committee (2019/676), the Scientific Committee of the Ministry of Science and Technology, Vietnam (08/QD-HDQL-NAFOSTED) and the Institutional Review Board of the National Lung Hospital, Vietnam (13/19/CT-HDDD). Study findings will be published in peer-reviewed journals and conference proceedings.

TRIAL REGISTRATION NUMBER: ACTRN12620000681954.

DOI: 10.1136/bmjopen-2023-076778
PMCID: PMC10729151
PMID: 38081668 [Indexed for MEDLINE]

Conflict of interest statement: Competing interests: None declared.

9. Discrepancy in the transmissibility of multidrug-resistant mycobacterium tuberculosis in urban and rural areas in China.

Emerg Microbes Infect. 2023 Dec;12(1):2192301. doi: 10.1080/22221751.2023.2192301.

Li M(1)(2), Lu L(3), Guo M(4), Jiang Q(5), Xia L(6), Jiang Y(7), Zhang S(6), Qiu Y(4), Yang C(1)(8), Chen Y(1)(2), Hong J(3), Guo X(3), Takiff H(9), Shen X(7), Chen C(6), Gao Q(1)(2).

The fitness of multidrug-resistant tuberculosis (MDR-TB) is thought to be an important determinant of a strain's ability to be transmitted. Studies in the laboratory have demonstrated that MDR-TB strains have reduced fitness but the relative transmissibility of MDR-TB versus drug-susceptible (DS) TB strains in human populations remains unresolved. We used data on genomic clustering from our previous molecular epidemiological study in Songjiang (2011-2020) and Wusheng (2009-2020), China, to compare the relative transmissibility of MDR-TB versus DS-TB. Genomic clusters were defined with a threshold distance of 12-single-nucleotide-polymorphisms and the risk for MDR-TB clustering was analyzed by logistic regression. In total, 2212 culture-positive pulmonary TB patients were enrolled in Songjiang and 1289 in Wusheng. The clustering rates of MDR-TB and DS-TB strains were 19.4% (20/103) and 26.3% (509/1936), respectively in Songjiang, and 43.9% (29/66) and 26.0% (293/1128) in Wusheng. The risk of MDR-TB clustering was 2.34 (95% CI 1.38-3.94) times higher than DS-TB clustering in Wusheng and 0.64 (95% CI 0.38-1.06) times lower in Songjiang. Neither lineage 2, compensatory mutations nor rpoB S450L were significantly associated with MDR-TB transmission, and katG S315 T increased MDR-TB transmission only in Wusheng (OR 5.28, 95% CI 1.42-19.21). MDR-TB was not more transmissible than DS-TB in either Songjiang or Wusheng. It appears that the different transmissibility of MDR-TB in Songjiang and Wusheng is likely due to differences in the quality of the local TB control programmes. Suggesting that the most effective way to control MDR-TB is by improving local TB control programmes.

DOI: 10.1080/22221751.2023.2192301
PMCID: PMC10062220
PMID: 36924242 [Indexed for MEDLINE]

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

10. Higher loss of livelihood and impoverishment in households affected by tuberculosis compared to non-tuberculosis affected households in Zimbabwe: a cross-sectional study.

medRxiv. 2023 Dec 5:2023.12.05.23299470. doi: 10.1101/2023.12.05.23299470. Preprint.

Timire C, Houben RM, Pedrazzoli D, Ferrand RA, Calderwood CJ, Bond V, Mbiba F, Kranzer K.

INTRODUCTION: Tuberculosis (TB) disproportionally affects poor people, leading to income and non-income losses. Measures of socioeconomic impact of TB, e.g. impoverishment and patient costs are inadequate to capture non-income losses. We applied impoverishment and a multidimensional measure on TB and non-TB affected households in Zimbabwe.

METHODS: We conducted a cross-sectional study in 270 households: 90 non-TB; 90 drug-susceptible TB (DS-TB), 90 drug-resistant TB (DR-TB) during the COVID-19 pandemic (2020-2021). Household data included ownership of assets, number of household members, income and indicators on five capital assets: financial, human, social, natural and physical. We determined proportions of impoverished households for periods 12 months prior and at the time of the interview. Households with incomes below US$1.90/day were considered to be impoverished. We used principal component analysis on five capital asset indicators to create a binary outcome variable indicating loss of livelihood. Log-binomial regression was used to determine associations between loss of livelihood and type of household.

RESULTS: TB-affected households reported higher previous episodes of TB and household members requiring care than non-TB households. Households that were impoverished 12 months prior to the study were: 21 non-TB (23%); 40 DS-TB (45%); 37 DR-TB (41%). The proportions increased to 81%, 88% and 94%, respectively by the time of interview. Overall, 56% (152/270) of households sold assets: 44% (40/90) non-TB, 58% (52/90) DS-TB and 67% (60/90) DR-TB. Children's education was affected in 31% (56/180) of TB-affected compared to 13% (12/90) non-TB households. Overall, 133(50%) households experienced loss of livelihood, with TB-affected households twice as likely to experience loss of livelihood; adjusted prevalence ratio (aPR=2.02 (95%CI:1.35-3.03)). The effect of TB on livelihood was most pronounced in poorest households (aPR=2.64, (95%CI:1.29-5.41)).

CONCLUSIONS: TB-affected households experienced greater socioeconomic losses compared to non-TB households. Multidimensional measures of TB are crucial to inform multisectoral approaches to mitigate impacts of TB and other shocks.

DOI: 10.1101/2023.12.05.23299470
PMCID: PMC10723493

PMID: 38106129

11. Health-seeking pathway of drug-resistant TB patients in Vadodara, India.

Public Health Action. 2023 Dec;13(4):155-161. doi: 10.5588/pha.23.0019. Epub 2023 Dec 7.

Sheth M(1), Shringarpure K(2)(3), Modi B(4), Damor R(2), Manikam L(3)(5).

BACKGROUND: Health-seeking behaviour refers to patients' choices regarding their preferred healthcare destination and the timing of seeking assistance for treatment. Patients with TB usually first approach the private sector and/or lose several months' time in inappropriate diagnosis and treatment due to lack of awareness regarding the availability of standard treatment protocols. This can lead to poor outcomes such as drug-resistant TB (DR-TB) and/or death.

METHODOLOGY: A cross-sectional study was conducted to examine the health-seeking pathway and delays in diagnosis and initiation of DR-TB treatment among patients registered with the DR-TB centre in Vadodara District (India).

RESULTS: A total of 93 patients were enrolled in the study; the median age was 35 years (IQR 24-45). For the first visit, 59 (63%) patients chose a public healthcare facility, mainly because the facility was near their residence (n = 20, 21.5%). The median delay in reaching the first healthcare facility was 12 days (IQR 7.5-30). Delay in reaching second- and third-level care was respectively 25 days (IQR 9-68) and 16 days (IQR 4-67).

CONCLUSION: Two-thirds of patients required visits to a second healthcare centre for diagnosis, while one third needed a third visit. The overall median delay for reaching the DR-TB centre was 60 days (IQR 26-122). The median duration from symptom onset to the first healthcare contact fell within the timeframe for screening symptoms in standard diagnosis.

DOI: 10.5588/pha.23.0019
PMCID: PMC10703132
PMID: 38077719

12. Designing molecular diagnostics for current tuberculosis drug regimens.

Emerg Microbes Infect. 2023 Dec;12(1):2178243. doi:

10.1080/22221751.2023.2178243.

Georghiou SB(1), de Vos M(1), Velen K(1), Miotto P(2), Colman RE(1)(3), Cirillo DM(2), Ismail N(4), Rodwell TC(1)(3), Suresh A(1), Ruhwald M(1).

Diagnostic development must occur in parallel with drug development to ensure the longevity of new treatment compounds. Despite an increasing number of novel and repurposed anti-tuberculosis compounds and regimens, there remains a large number of drugs for which no rapid and accurate molecular diagnostic option exists. The lack of rapid drug susceptibility testing for linezolid, bedaquiline, clofazimine, the nitroimidazoles (i.e pretomanid and delamanid) and pyrazinamide at any level of the healthcare system compromises the effectiveness of current tuberculosis and drug-resistant tuberculosis treatment regimens. In the context of current WHO tuberculosis treatment guidelines as well as promising new regimens, we identify the key diagnostic gaps for initial and follow-on tests to diagnose emerging drug resistance and aid in regimen selection. Additionally, we comment on potential gene targets for inclusion in rapid molecular drug susceptibility assays and sequencing assays for novel and repurposed drug compounds currently prioritized in current regimens, and evaluate the feasibility of mutation detection given the design of existing technologies. Based on current knowledge, we also propose design priorities for next generation molecular assays to support triage of tuberculosis patients to appropriate and effective treatment regimens. We encourage assay developers to prioritize development of these key molecular assays and support the continued evolution, uptake, and utility of sequencing to build knowledge of tuberculosis resistance mechanisms and further inform rapid treatment decisions in order to curb resistance to critical drugs in current regimens and achieve End TB targets.Trial registration: ClinicalTrials.gov identifier: NCT05117788..

DOI: 10.1080/22221751.2023.2178243
PMCID: PMC9980415
PMID: 36752055 [Indexed for MEDLINE]

Conflict of interest statement: SBG, MdV, KV, REC, TCR, AS and MR are consultants or employees of FIND, the global alliance for diagnostics, a not-for-profit foundation that supports the evaluation of publicly prioritized TB assays and the implementation of WHO-approved (guidance and prequalification) assays using donor grants. FIND has product evaluation agreements with several private sector companies that design diagnostics for TB and other diseases. These agreements strictly define FIND's independence and neutrality with regard to these private sector companies. MR, PM and DMC are members of the NDWG StopTB Partnership. TCR is a cofounder, board member, and shareholder of Verus Diagnostics, a company that was founded with the intent of developing diagnostic assays. Verus Diagnostics was not involved in any way with data collection,

analysis or publication of the results, and TCR has not received any financial support from Verus Diagnostics. University of California, San Diego (UCSD) Conflict of Interest office has reviewed and approved TCR's role in Verus Diagnostics. TCR is a coinventor of a provisional patent for a TB diagnostic assay (provisional patent 63/048.989). TCR is also a coinventor on a patent associated with the processing of TB sequencing data (European Patent Application No. 14840432.0 & USSN 14/912,918), and has agreed to "donate all present and future interest in and rights to royalties from this patent" to UCSD to ensure that he does not receive any financial benefits from this patent.

13. Survival status and risk factors for mortality among multidrug-resistant tuberculosis patients in Addis Ababa, Ethiopia: A retrospective follow-up study.

J Clin Tuberc Other Mycobact Dis. 2023 Sep 19;33:100398. doi: 10.1016/j.jctube.2023.100398. eCollection 2023 Dec.

Getahun GK(1), Gezahegn E(2), Endazenawe G(3), Shitemaw T(2), Negash Z(3), Dessu S(4).

BACKGROUND: Tuberculosis continues to be a major health concern around the world. It kills an estimated 1.6 million people each year. The World Health Organization (WHO) removed Ethiopia from its list of thirty countries having a high prevalence of MDR/RR-TB in 2021. As a result, the aim of this study was to assess the current context of survival status and risk factors of multidrug-resistant tuberculosis patients in Addis Ababa, Ethiopia, in 2022.

METHODS: An institutional-based retrospective cohort study with 245 patients was undertaken using multidrug-resistant tuberculosis patients who were recruited from January 1st, 2018 to December 30th, 2021, in St. Peter's specialized hospital. To find independent predictors of survival status, Cox regression analysis was used. An adjusted hazard ratio with a 95% confidence interval and a p-value of < 0.05 was used to establish association and statistical significance.

RESULTS: The result of the study revealed that the incidence of mortality in this study was 13.1% (95% CI: 10.3-16.5). Moreover, being male (AOR = 3.7: 95% CI = 1.2, 11.4), old age (AOR = 14: 95% CI = 3.0, 60.4), site of TB (AOR = 0.2: 95% CI = 0.03, 0.6), and presence of comorbidity (AOR = 9.2: 95% CI = 2.4, 35.3), were independent predictors of time to death.

CONCLUSION: Generally, the death rate among research participants was high. Moreover, male gender, old age, site of tuberculosis, and presence of other comorbidity were predictors of mortality among MDR-TB patients.

DOI: 10.1016/j.jctube.2023.100398
PMCID: PMC10520522
PMID: 37767135

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.

14. Isoniazid resistance-conferring mutations are associated with highly variable phenotypic resistance.

J Clin Tuberc Other Mycobact Dis. 2023 Jul 26;33:100387. doi: 10.1016/j.jctube.2023.100387. eCollection 2023 Dec.

Lale Ngema S(1), Dookie N(1), Perumal R(1)(2), Nandlal L(1), Naicker N(1), Peter Letsoalo M(1), O'Donnell M(3), Khan A(1), Padayatchi N(1), Naidoo K(1)(2).

BACKGROUND: High-dose isoniazid is recommended in the 9-12 months short-course regimen for multidrug-resistant tuberculosis with inhA mutation. However, there is insufficient evidence to support the assumption of genotypic-phenotypic concordance. This study aimed to identify the genetic mutations associated with high-level phenotypic isoniazid resistance.

METHODS: Clinical isolates from patients with drug-resistant tuberculosis were profiled by whole-genome sequencing and subjected to minimum inhibitory concentration (MIC) testing using MGIT based-method. MICs were performed in concentration ranges based on the mutation present: isolates with no isoniazid resistance-conferring mutations and H37Rv, 0.016-0.256 µg/ml; inhA, 0.256-4.0 µg/ml, katG 1.0-16.0 µg/ml; and inhA + katG, 4.0-64.0 µg/ml. Isolates demonstrating resistance at the upper limit of the concentration range were tested up to the maximum of 64.0 µg/ml. Bootstrap of the mean MICs was performed to increase the robustness of the estimates and an overlap index was used to compare the distributions of the MICs for each mutation profile.

RESULTS: A total of 52 clinical isolates were included in this analysis. Bootstrap MIC means for inhA, katG and inhA + katG were 33.64 (95% CI, 9.47, 56.90), 6.79 (4.45, 9.70) and 52.34 (42.750, 61.66) µg/ml, respectively. There was high overlap between inhA and inhA + katG mutations (eta = 0.45) but not with inhA and katG (eta = 0.19). Furthermore, katG showed poor overlap with inhA + katG mutations (eta = 0.09). Unexpectedly, 4/8 (50.0%) of all InhA mutants demonstrated high-level resistance, while 20/24 (83.3%) of katG mutants

demonstrated moderate-level resistance.

CONCLUSIONS: InhA mutations demonstrated unexpectedly high MICs and showed high overlap with inhA + katG. Contrary to the common belief that katG mutants are associated with high-level resistance, this mutation primarily showed moderate-level resistance.

DOI: 10.1016/j.jctube.2023.100387
PMCID: PMC10405055
PMID: 37554582

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.

15. Bedaquiline resistance in patients with drug-resistant tuberculosis in Cape Town, South Africa: a retrospective longitudinal cohort study.

Lancet Microbe. 2023 Dec;4(12):e972-e982. doi: 10.1016/S2666-5247(23)00172-6. Epub 2023 Nov 3.

Derendinger B(1), Dippenaar A(2), de Vos M(3), Huo S(4), Alberts R(1), Tadokera R(1), Limberis J(5), Sirgel F(1), Dolby T(6), Spies C(1), Reuter A(7), Folkerts M(8), Allender C(8), Lemmer D(8), Van Rie A(9), Gagneux S(10), Rigouts L(11), Te Riele J(12), Dheda K(13), Engelthaler DM(8), Warren R(1), Metcalfe J(5), Cox H(14), Theron G(15).

BACKGROUND: Bedaquiline is a life-saving tuberculosis drug undergoing global scale-up. People at risk of weak tuberculosis drug regimens are a priority for novel drug access despite the potential source of Mycobacterium tuberculosis-resistant strains. We aimed to characterise bedaquiline resistance in individuals who had sustained culture positivity during bedaquiline-based treatment.

METHODS: We did a retrospective longitudinal cohort study of adults (aged ≥18 years) with culture-positive pulmonary tuberculosis who received at least 4 months of a bedaquiline-containing regimen from 12 drug-resistant tuberculosis treatment facilities in Cape Town, South Africa, between Jan 20, 2016, and Nov 20, 2017. Sputum was programmatically collected at baseline (ie, before bedaquiline initiation) and each month to monitor treatment response per the national algorithm. The last available isolate from the sputum collected at or

after 4 months of bedaquiline was designated the follow-up isolate. Phenotypic drug susceptibility testing for bedaquiline was done on baseline and follow-up isolates in MGIT960 media (WHO-recommended critical concentration of 1 μg/mL). Targeted deep sequencing for Rv0678, atpE, and pepQ, as well as whole-genome sequencing were also done.

FINDINGS: In total, 40 (31%) of 129 patients from an estimated pool were eligible for this study. Overall, three (8%) of 38 patients assessable by phenotypic drug susceptibility testing for bedaquiline had primary resistance, 18 (47%) gained resistance (acquired or reinfection), and 17 (45%) were susceptible at both baseline and follow-up. Several Rv0678 and pepQ single-nucleotide polymorphisms and indels were associated with resistance. Although variants occurred in Rv0676c and Rv1979c, these variants were not associated with resistance. Targeted deep sequencing detected low-level variants undetected by whole-genome sequencing; however, none were in genes without variants already detected by whole-genome sequencing. Patients with baseline fluoroquinolone resistance, clofazimine exposure, and four or less effective drugs were more likely to have bedaquiline-resistant gain. Resistance gain was primarily due to acquisition; however, some reinfection by resistant strains occurred.

INTERPRETATION: Bedaquiline-resistance gain, for which we identified risk factors, was common in these programmatically treated patients with sustained culture positivity. Our study highlights risks associated with implementing life-saving new drugs and shows evidence of bedaquiline-resistance transmission. Routine drug susceptibility testing should urgently accompany scale-up of new drugs; however, rapid drug susceptibility testing for bedaquiline remains challenging given the diversity of variants observed.

FUNDING: Doris Duke Charitable Foundation, US National Institute of Allergy and Infectious Diseases, South African Medical Research Council, National Research Foundation, Research Foundation Flanders, Stellenbosch University Faculty of Medicine Health Sciences, South African National Research Foundation, Swiss National Science Foundation, and Wellcome Trust.

DOI: 10.1016/S2666-5247(23)00172-6
PMID: 37931638 [Indexed for MEDLINE]

Conflict of interest statement: Declaration of interests We declare no competing interests.

16. Dynamics of tuberculosis infection in various populations during the 19th and 20th century: The impact of conservative and pharmaceutical treatments.

Tuberculosis (Edinb). 2023 Dec;143S:102389. doi: 10.1016/j.tube.2023.102389. Epub 2023 Nov 25.

Holloway-Kew KL(1), Henneberg M(2).

Humans and Mycobacterium tuberculosis have co-evolved together for thousands of years. Many individuals are infected with the bacterium, but few show signs and symptoms of tuberculosis (TB). Pharmacotherapy to treat those who develop disease is useful, but drug resistance and non-adherence significantly impact the efficacy of these treatments. Prior to the introduction of antibiotic therapies, public health strategies were used to reduce TB mortality. This work shows how these strategies were able to reduce TB mortality in 19th and 20th century populations, compared with antibiotic treatments. Previously published mortality data from historical records for several populations (Switzerland, Germany, England and Wales, Scotland, USA, Japan, Brazil and South Africa) were used. Curvilinear regression was used to examine the reduction in mortality before and after the introduction of antibiotic treatments (1946). A strong decline in TB mortality was already occurring in Switzerland, Germany, England and Wales, Scotland and the USA prior to the introduction of antibiotic treatment. This occurred following many public health interventions including improved sanitation, compulsory reporting of TB cases, diagnostic techniques and sanatoria treatments. Following the introduction of antibiotics, mortality rates declined further, however, this had a smaller effect than the previously employed strategies. In Japan, Brazil and South Africa, reductions in mortality rates were largely driven by antibiotic treatments that caused rapid decline of mortality, with a smaller contribution from public health strategies. For the development of active disease, immune status is important. Individuals infected with the bacterium are more likely to develop signs and symptoms if their immune function is reduced. Effective strategies against TB can therefore include enhancing immune function of the population by improving nutrition, as well as reducing transmission by improving living conditions and public health. This has been effective in the past. Improving immunity may be an important strategy against drug resistant TB.

DOI: 10.1016/j.tube.2023.102389
PMID: 38012934 [Indexed for MEDLINE]

Conflict of interest statement: Declarations of competing interest None.

17. Discovery of pyrimidine-tethered benzothiazole derivatives as novel anti-tubercular agents towards multi- and extensively drug resistant Mycobacterium tuberculosis.

J Enzyme Inhib Med Chem. 2023 Dec;38(1):2250575. doi: 10.1080/14756366.2023.2250575.

Hemeda LR(1), El Hassab MA(2), Abdelgawad MA(3)(4), Khaleel EF(5), Abdel-Aziz MM(6), Binjubair FA(7), Al-Rashood ST(7), Eldehna WM(8)(9), El-Ashrey MK(2)(10).

In this study, new benzothiazole-pyrimidine hybrids (5a-c, 6, 7a-f, and 8-15) were designed and synthesised. Two different functionalities on the pyrimidine moiety of lead compound 4 were subjected to a variety of chemical changes with the goal of creating various functionalities and cyclisation to further elucidate the target structures. The potency of the new molecules was tested against different tuberculosis (TB) strains. The results indicated that compounds 5c, 5b, 12, and 15 (MIC = 0.24-0.98 µg/mL) are highly active against the first-line drug-sensitive strain of Mycobacterium tuberculosis (ATCC 25177). Thereafter, the anti-tubercular activity was evaluated against the two drug-resistant TB strains; ATCC 35822 and RCMB 2674, where, many compounds exhibited good activity with MIC = 0.98-62.5 3 µg/mL and 3.9-62.5 µg/mL, respectively. Compounds 5c and 15 having the highest anti-tubercular efficiency towards sensitive strain, displayed the best activity for the resistant strains by showing the MIC = 0.98 and 1.95 µg/mL for MDR TB, and showing the MIC = 3.9 and 7.81 µg/mL for XDR TB, consecutively. Finally, molecular docking studies were performed for the two most active compounds 5c and 15 to explore their enzymatic inhibitory activities.

DOI: 10.1080/14756366.2023.2250575
PMCID: PMC10472891
PMID: 37649381 [Indexed for MEDLINE]

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

18. The rare manifestations in tuberculous meningoencephalitis: a review of available literature.

Ann Med. 2023 Dec;55(1):342-347. doi: 10.1080/07853890.2022.2164348.

He RL(1), Liu Y(1), Tan Q(1), Wang L(1).

Aim: Tuberculous meningitis is an infectious disease of the central nervous system caused by Mycobacterium tuberculosis (M. tuberculosis). It mainly involves the meninges and brain parenchyma, as well as the spinal cord and meninges; Disability and mortality rates are high. In recent years, due to the increase of drug-resistant tuberculosis patients, population mobility and the prevalence of acquired immune deficiency syndrome, the incidence rate of tuberculosis has increased significantly, and tuberculous meningitis has also increased.

Methods: At present, tuberculosis is still a worldwide infectious disease that seriously threatens human health, especially in underdeveloped and developing countries. China is the largest developing country in the world with a large population.

Results: The situation of tuberculosis prevention and control is grim. Its disability rate is the highest in tuberculosis infection. In addition to the common non-specific manifestations, tuberculous meningoencephalitis may also have rare manifestations of stroke, hearing loss and visual loss.

Conclusion: Understanding and timely improvement of corresponding examinations and targeted treatment will help improve the prognosis of patients.

DOI: 10.1080/07853890.2022.2164348
PMCID: PMC9828632
PMID: 36598144 [Indexed for MEDLINE]

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

19. Descriptors of multidrug-resistant TB deaths in Ethiopia.

Public Health Action. 2023 Dec;13(4):123-125. doi: 10.5588/pha.23.0030. Epub 2023 Dec 7.

Tesema E(1), Dememew ZG(2), Datiko DG(2), Gebreyohannes A(1), Molla Y(2), Tefera A(1), Gizatie G(1), Bogale T(1), Million M(1), Suarez PG(3), Aseressa MM(3), Jerene D(4), Biru M(1).

Deaths related to multidrug-resistant TB among patients who had received a second-line anti-TB drugs in Ethiopia were analysed. Respectively 38/704 (5.4%)

and 44/995 (4.4%) deaths were identified in two cohorts (2015 and 2022). In the 2015 cohort, severe malnutrition was less prevalent, previous treatment rates were three times higher, hypokalaemia was more frequent, and the use of the Xpert® MTB/RIF assay, respiratory failure and severe anaemia/pancytopenia were less common than in the 2022 cohort. We observed that there were variations in adverse events when different treatment regimens were used over different time periods. To ensure proper patient care, correct guidance must be consistently implemented.

DOI: 10.5588/pha.23.0030
PMCID: PMC10703136
PMID: 38077723

20. Predictive capabilities of baseline radiological findings for early and late disease outcomes within sensitive and multi-drug resistant tuberculosis cases.

Eur J Radiol Open. 2023 Sep 27;11:100518. doi: 10.1016/j.ejro.2023.100518. eCollection 2023 Dec.

Rosenfeld G(1), Gabrielian A(1), Hurt D(1), Rosenthal A(1).

PURPOSE: This study compares performance of Timika Score to standardized, detailed radiologist observations of Chest X rays (CXR) for predicting early infectiousness and subsequent treatment outcome in drug sensitive (DS) or multi-drug resistant (MDR) tuberculosis cases. It seeks improvement in prediction of these clinical events through these additional observations.

METHOD: This is a retrospective study analyzing cases from the NIH/NIAID supported TB Portals database, a large, trans-national, multi-site cohort of primarily drug-resistant tuberculosis patients. We analyzed patient records with sputum microscopy readings, radiologist annotated CXR, and treatment outcome including a matching step on important covariates of age, gender, HIV status, case definition, Body Mass Index (BMI), smoking, drug use, and Timika Score across resistance type for comparison.

RESULTS: 2142 patients with tuberculosis infection (374 with poor outcome and 1768 with good treatment outcome) were retrospectively reviewed. Bayesian ANOVA demonstrates radiologist observations did not show greater predictive ability for baseline infectiousness (0.77 and 0.74 probability in DS and MDR respectively); however, the observations provided superior prediction of treatment outcome (0.84 and 0.63 probability in DS and MDR respectively). Estimated lung abnormal area and cavity were identified as important predictors

underlying the Timika Score's performance.

CONCLUSIONS: Timika Score simplifies the usage of baseline CXR for prediction of early infectiousness of the case and shows comparable performance to using detailed, standardized radiologist observations. The score's utility diminishes for treatment outcome prediction and is exceeded by the usage of the detailed observations although prediction performance on treatment outcome decreases especially in MDR TB cases.

DOI: 10.1016/j.ejro.2023.100518
PMCID: PMC10556559
PMID: 37808069

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. Tuberculosis in Ukrainian War Refugees and Migrants in the Czech Republic and Slovakia: A Molecular Epidemiological Study.

J Epidemiol Glob Health. 2023 Dec 4. doi: 10.1007/s44197-023-00166-5. Online ahead of print.

Dohál M(1), Dvořáková V(2), Šperková M(2), Pinková M(2), Ghodousi A(3)(4)(5), Omrani M(3), Porvazník I(6)(7), Rasmussen EM(8), Škereňová M(9), Krivošová M(9), Wallenfels J(10), Konstantynovska O(11), Walker TM(12)(13), Nikolayevskyy V(14), Cirillo DM(3), Solovič I(6)(7), Mokrý J(9).

BACKGROUND: The war in Ukraine has led to significant migration to neighboring countries, raising public health concerns. Notable tuberculosis (TB) incidence rates in Ukraine emphasize the immediate requirement to prioritize approaches that interrupt the spread and prevent new infections.

METHODS: We conducted a prospective genomic surveillance study to assess migration's impact on TB epidemiology in the Czech Republic and Slovakia. Mycobacterium tuberculosis isolates from Ukrainian war refugees and migrants, collected from September 2021 to December 2022 were analyzed alongside 1574 isolates obtained from Ukraine, the Czech Republic, and Slovakia.

RESULTS: Our study revealed alarming results, with historically the highest number of Ukrainian tuberculosis patients detected in the host countries. The

increasing number of cases of multidrug-resistant TB, significantly linked with Beijing lineage 2.2.1 ($p < 0.0001$), also presents substantial obstacles to control endeavors. The genomic analysis identified the three highly related genomic clusters, indicating the recent TB transmission among migrant populations. The largest clusters comprised war refugees diagnosed in the Czech Republic, TB patients from various regions of Ukraine, and incarcerated individuals diagnosed with pulmonary TB specialized facility in the Kharkiv region, Ukraine, pointing to a national transmission sequence that has persisted for over 14 years.

CONCLUSIONS: The data showed that most infections were likely the result of reactivation of latent disease or exposure to TB before migration rather than recent transmission occurring within the host country. However, close monitoring, appropriate treatment, careful surveillance, and social support are crucial in mitigating future risks, though there is currently no evidence of local transmission in EU countries.

DOI: 10.1007/s44197-023-00166-5
PMID: 38048026

22. The economic burden of households affected by tuberculosis in Brazil: First national survey results, 2019-2021.

PLoS One. 2023 Dec 13;18(12):e0287961. doi: 10.1371/journal.pone.0287961. eCollection 2023.

Noia Maciel EL(1), Negri LDSA(2), Guidoni LM(2), Fregona GC(3), Johansen FDC(4), Sanchez MN(5), Moreira ADSR(6), Diaz-Quijano FA(7), Tonini M(5), Zandonade E(8), Ershova J(9), Nguhiu P(10), Baena IG(11).

BACKGROUND: One of the three main targets of the World Health Organization (WHO) End TB Strategy (2015-2035) is that no tuberculosis (TB) patients or their households face catastrophic costs (defined as exceeding 20% of the annual household income) because of the disease. Our study seeks to determine, as a baseline, the magnitude and main drivers of the costs associated with TB disease for patients and their households and to monitor the proportion of households experiencing catastrophic costs in Brazil.

METHODS: A national cross-sectional cluster-based survey was conducted in Brazil in 2019-2021 following WHO methodology. TB patients of all ages and types of TB were eligible for the survey. Adult TB patients and guardians of minors (<18 years old) were interviewed once about costs, time loss, coping measures,

income, household expenses, and asset ownership. Total costs, including indirect costs measured as reported household income change, were expressed as a percentage of annual household income. We used descriptive statistics to analyze the cost drivers and multivariate logistic regression to determine factors associated with catastrophic costs.

RESULTS: We interviewed 603 patients, including 538 (89%) with drug-sensitive (DS) and 65 (11%) with drug-resistant (DR) TB. Of 603 affected households, 48.1% (95%CI: 43-53.2) experienced costs above 20% of their annual household income during their TB episode. The proportion was 44.4% and 78.5% among patients with DS- and DR-TB, respectively. On average, patients incurred costs of US$1573 (95%CI: 1361.8-1785.0) per TB episode, including pre-diagnosis and post-diagnosis expenses. Key cost drivers were post-diagnosis nutritional supplements (US$317.6, 95%CI: 232.7-402.6) followed by medical costs (US$85.5, 95%CI: 54.3-116.5) and costs of travel for clinic visits during treatment (US$79.2, 95%CI: 61.9-96.5). In multivariate analysis, predictors of catastrophic costs included positive HIV status (aOR = 3.0, 95%CI:1.1-8.6) and self-employment (aOR = 2.7, 95%CI:1.1-6.5); high education was a protective factor (aOR = 0.1, 95%CI:0.0-0.9).

CONCLUSIONS: Although the services offered to patients with TB are free of charge in the Brazilian public health sector, the availability of free diagnosis and treatment services does not alleviate patients' financial burden related to accessing TB care. The study allowed us to identify the costs incurred by patients and suggest actions to mitigate their suffering. In addition, this study established a baseline for monitoring catastrophic costs and fostering a national policy to reduce the costs to patients for TB care in Brazil.

DOI: 10.1371/journal.pone.0287961
PMCID: PMC10718450
PMID: 38091306 [Indexed for MEDLINE]

Conflict of interest statement: JE works for the CDC and participated in the elaboration of the initial proposal and in the writing of the article, but neither she nor the agency had a decision on the analysis of the data and the publication of the research.

23. Bedaquiline, Delamanid, Linezolid, Clofazimine, and Capreomycin MIC

Distributions for Drug Resistance Mycobacterium tuberculosis in Shanghai, China.

Infect Drug Resist. 2023 Dec 11;16:7587-7595. doi: 10.2147/IDR.S440711.
eCollection 2023.

Guo Y(1), Yang J(1), Wang W(1), Wu X(1), Wan B(1), Wang H(1), Sha W(2), Yu F(1).

BACKGROUND: New antituberculosis drugs have recently been approved for the treatment of multidrug-resistant tuberculosis TB (MDR-TB). We aimed to describe the distributions of bedaquiline, delamanid, linezolid, clofazimine, and capreomycin MIC values for M. tuberculosis.

METHODS: M. tuberculosis clinical isolates were originally isolated from 2020 to 2021 from 1452 different pulmonary tuberculosis patients of the Shanghai Pulmonary Hospital in China. The drug susceptibility testing was performed using the Sensititre custom plates (SHTBMY) (TREK Diagnostic Systems, Thermo Fisher Scientific In., USA) consisting of a 96-well microtitre plate containing 4 (bedaquiline, delamanid, clofazimine, capreomycin) antimicrobial agents. MICs were determined for linezolid using a microdilution method.

RESULTS: Based on the latest definitions, 156 (10.74%) were MDR-TB, 93 (6.40%) were pre-XDR-TB, and 27 (1.86%) were XDR-TB. The rate of BDQ resistance in cases of MDR-TB was 7.69%, while it was observed to be 10.75% in cases of pre-XDR-TB, and significantly higher at 37.04% in cases of XDR-TB. The lowest rate of drug resistance against M. tuberculosis was DLM (0.14%). For LZD, 11 (0.76%) clinical isolates were resistant, based on the CLSI breakpoint of 1μg/mL. The five strains with a MIC value of >32 for LZD resistance were XDR-TB isolates. Among all MDR, pre-XDR, and XDR isolates tested, LZD' MIC50 increased from 0.25 and 0.5 to 1μg/mL. The MIC90 value of LZD against XDR-TB isolates was 32μg/mL. For CFZ, six isolates with elevated MICs of ≥2μg/mL. CFZ's MIC50 and MIC90 values in all isolates were 0.12μg/mL and 0.25μg/mL, respectively.

CONCLUSION: The study findings indicate that BDQ, DLM, CFZ, and LZD may exhibited excellent in vitro activity against MDR-TB isolates. Detection of resistance to BDQ and LZD was alarming for XDR-TB isolates. It is necessary to perform universal drug sensitivity testing for M. tuberculosis, especially MDR-TB and XDR-TB patients.

DOI: 10.2147/IDR.S440711
PMCID: PMC10723587
PMID: 38107433

Conflict of interest statement: No potential conflict of interest was reported by the authors.

24. Adaptive evaluation of mHealth and conventional adherence support interventions to optimize outcomes with new treatment regimens for drug-resistant tuberculosis and HIV in South Africa (ADAP-TIV): study protocol for an adaptive randomized controlled trial.

Trials. 2023 Dec 1;24(1):776. doi: 10.1186/s13063-023-07520-9.

Ross J(1), Perumal R(2), Wolf A(1), Zulu M(2), Guzman K(1), Seepamore B(2)(3), Reis K(4), Nyilana H(2), Hlathi S(2), Narasimmulu R(2), Cheung YKK(5), Amico KR(6), Friedland G(7), Daftary A(2)(8), Zelnick JR(9), Naidoo K(2), O'Donnell MR(10)(11)(12).

Update of
Res Sq. 2023 Jun 09;:

BACKGROUND: Highly effective, short-course, bedaquiline-containing treatment regimens for multidrug-resistant tuberculosis (MDR-TB) and integrase strand transfer inhibitor (INSTI)-containing fixed dose combination antiretroviral therapy (ART) have radically transformed treatment for MDR-TB and HIV. However, without advances in adherence support, we may not realize the full potential of these therapeutics. The primary objective of this study is to compare the effect of adherence support interventions on clinical and biological endpoints using an adaptive randomized platform.

METHODS: This is a prospective, adaptive, randomized controlled trial comparing the effectiveness of four adherence support strategies on a composite clinical outcome in adults with MDR-TB and HIV initiating bedaquiline-containing MDR-TB treatment regimens and receiving ART in KwaZulu-Natal, South Africa. Trial arms include (1) enhanced standard of care, (2) psychosocial support, (3) mHealth using cellular-enabled electronic dose monitoring, and (4) combined mHealth and psychosocial support. The level of support will be titrated using a differentiated service delivery (DSD)-informed assessment of treatment support needs. The composite primary outcome will include survival, negative TB culture, retention in care, and undetectable HIV viral load at month 12. Secondary outcomes will include individual components of the primary outcome and quantitative evaluation of adherence on TB and HIV treatment outcomes.

DISCUSSION: This trial will evaluate the contribution of different modes of adherence support on MDR-TB and HIV outcomes with WHO-recommended all-oral MDR-TB regimens and ART in a high-burden operational setting. We will also

assess the utility of a DSD framework to pragmatically adjust levels of MDR-TB and HIV treatment support.

TRIAL REGISTRATION: ClinicalTrials.gov NCT05633056. Registered on 1 December 2022.

DOI: 10.1186/s13063-023-07520-9
PMCID: PMC10691086
PMID: 38037105 [Indexed for MEDLINE]

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

25. Determinants of catastrophic costs among households affected by multi-drug resistant tuberculosis in Ho Chi Minh City, Viet Nam: a prospective cohort study.

BMC Public Health. 2023 Dec 3;23(1):2372. doi: 10.1186/s12889-023-17078-5.

Pham TAM(1), Forse R(2)(3), Codlin AJ(1)(4), Phan THY(5), Nguyen TT(5), Nguyen N(4), Vo LNQ(5), Dat PT(6), Minh HDT(6), Nguyen LH(6), Nguyen HB(7), Nguyen NV(7)(8), Bodfish M(9), Lönnroth K(1), Wingfield T(1)(10)(11), Annerstedt KS(1).

BACKGROUND: Globally, most people with multidrug-resistant tuberculosis (MDR-TB) and their households experience catastrophic costs of illness, diagnosis, and care. However, the factors associated with experiencing catastrophic costs are poorly understood. This study aimed to identify risk factors associated with catastrophic costs incurrence among MDR-TB-affected households in Ho Chi Minh City (HCMC), Viet Nam.

METHODS: Between October 2020 and April 2022, data were collected using a locally-adapted, longitudinal WHO TB Patient Cost Survey in ten districts of HCMC. Ninety-four people with MDR-TB being treated with a nine-month TB regimen were surveyed at three time points: after two weeks of treatment initiation, completion of the intensive phase and the end of the treatment (approximately five and 10 months post-treatment initiation respectively). The catastrophic costs threshold was defined as total TB-related costs exceeding 20% of annual pre-TB household income. Logistic regression was used to identify variables associated with experiencing catastrophic costs. A sensitivity analysis examined the prevalence of catastrophic costs using alternative thresholds and cost estimation approaches.

RESULTS: Most participants (81/93 [87%]) experienced catastrophic costs despite the majority 86/93 (93%) receiving economic support through existing social protection schemes. Among participant households experiencing and not experiencing catastrophic costs, median household income was similar before MDR-TB treatment. However, by the end of MDR-TB treatment, median household income was lower (258 [IQR: 0-516] USD vs. 656 [IQR: 462-989] USD; p = 0.003), and median income loss was higher (2838 [IQR: 1548-5418] USD vs. 301 [IQR: 0-824] USD; p < 0.001) amongst the participant households who experienced catastrophic costs. Being the household's primary income earner before MDR-TB treatment (aOR = 11.2 [95% CI: 1.6-80.5]), having a lower educational level (aOR = 22.3 [95% CI: 1.5-344.1]) and becoming unemployed at the beginning of MDR-TB treatment (aOR = 35.6 [95% CI: 2.7-470.3]) were associated with experiencing catastrophic costs.

CONCLUSION: Despite good social protection coverage, most people with MDR-TB in HCMC experienced catastrophic costs. Incurrence of catastrophic costs was independently associated with being the household's primary income earner or being unemployed. Revision and expansion of strategies to mitigate TB-related catastrophic costs, in particular avoiding unemployment and income loss, are urgently required.

DOI: 10.1186/s12889-023-17078-5
PMCID: PMC10693707
PMID: 38042797 [Indexed for MEDLINE]

Conflict of interest statement: CDC Foundation played no role in the design of the study and collection, and analysis of data; however, one of the authors was employed by this funder and assisted with interpretation of data and editing of the manuscript. No other funding bodies played a role in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript.

26. Treatment outcomes and risk factors for an unsuccessful outcome among patients with highly drug-resistant tuberculosis in Ukraine.

Clin Microbiol Infect. 2023 Dec 6:S1198-743X(23)00574-8. doi: 10.1016/j.cmi.2023.12.001. Online ahead of print.

Pedersen OS(1), Butova T(2), Kapustnyk V(3), Miasoiedov V(3), Kuzhko M(4), Hryshchuk L(5), Kornaha S(5), Borovok N(6), Raznatovska O(7), Fedorec A(8), Bogomolov A(9), Tkhorovskiy M(9), Akymenko O(6), Klymenko I(10), Kulykova O(11),

Karpenko Z(12), Shapoval T(12), Chursina N(13), Kondratyuk N(14), Parkhomenko O(15), Sazonenko I(16), Ostrovskyy M(17), Makoida I(17), Markovtsiy L(18), Skryp V(18), Lubenko V(19), Hrankina N(20), Bondarenko L(21), Hlynenko V(22), Dahl VN(23), Butov D(24).

OBJECTIVES: To describe demographics, clinical features, and treatment outcomes of patients with highly drug-resistant tuberculosis (TB) in Ukraine, and to evaluate risk factors for an unsuccessful outcome.

METHODS: Data from patients with multi-, pre-extensively, or extensively drug-resistant TB were collected prospectively from TB dispensaries in 15 out 24 Ukrainian oblasts (regions) from 2020 to 2021. Treatment outcomes were evaluated using WHO definitions. Risk factors for an unsuccessful outcome were identified using a multivariable logistic regression model.

RESULTS: Among 1748 patients, the overall proportion of successful outcomes was 58% (95% confidence interval [95%CI] 56-60) (n=1015/1748), ranging from 65% (95%CI 62-69) (n=531/814) for multidrug-resistant TB to 54% (95%CI 49-58) (n=301/563) for pre-extensively drug-resistant TB and 49% (95%CI 44-55) (n=183/371) for extensively drug-resistant TB. Results were similar across oblasts, with few exceptions. The strongest risk factors for an unsuccessful outcome were extensively drug-resistant TB (adjusted OR [aOR] 3.23; 95%CI 1.88-5.53), total serum protein below 62 g/L in adults and below 57 g/L for children and adolescents (aOR 2.79; 95%CI 1.93-4.04), psychiatric illness (aOR 2.79; 95%CI 1.46, 5.33), age at TB diagnosis > 65 years (aOR 2.50; 95%CI 1.42-4.42), and alcohol misuse (aOR 2.48; 95%CI 1.89-3.26).

CONCLUSIONS: The overall proportion of successful outcomes among Ukrainians treated for highly drug-resistant TB was 58%, notably better compared with previous years, but still low for extensively drug-resistant TB. Risk factors for unsuccessful outcomes highlight that addressing socioeconomic factors in TB management is crucial. Efforts in maintaining TB dispensaries during and following the ongoing war are highly warranted.

DOI: 10.1016/j.cmi.2023.12.001
PMID: 38065363

27. Association between fatty acid metabolism gene mutations and Mycobacterium tuberculosis transmission revealed by whole genome sequencing.

BMC Microbiol. 2023 Dec 1;23(1):379. doi: 10.1186/s12866-023-03072-9.

Li Y(1), Kong X(2), Li Y(3), Tao N(4), Wang T(1), Li Y(1), Hou Y(1), Zhu X(5), Han Q(5), Zhang Y(5), An Q(4), Liu Y(6), Li H(7)(8).

BACKGROUND: Fatty acid metabolism greatly promotes the virulence and pathogenicity of Mycobacterium tuberculosis (M.tb). However, the regulatory mechanism of fatty acid metabolism in M.tb remains to be elucidated, and limited evidence about the effects of gene mutations in fatty acid metabolism on the transmission of M.tb was reported.

RESULTS: Overall, a total of 3193 M.tb isolates were included in the study, of which 1596 (50%) were genomic clustered isolates. Most of the tuberculosis isolates belonged to lineage2(n = 2744,85.93%), followed by lineage4(n = 439,13.75%) and lineage3(n = 10,0.31%).Regression results showed that the mutations of gca (136,605, 317G > C, Arg106Pro; OR, 22.144; 95% CI, 2.591-189.272), ogt(1,477,346, 286G > C ,Gly96Arg; OR, 3.893; 95%CI, 1.432-10.583), and rpsA (1,834,776, 1235 C > T, Ala412Val; OR, 3.674; 95% CI, 1.217-11.091) were significantly associated with clustering; mutations in gca and rpsA were also significantly associated with clustering of lineage2. Mutation in arsA(3,001,498, 885 C > G, Thr295Thr; OR, 6.278; 95% CI, 2.508-15.711) was significantly associated with cross-regional clusters. We also found that 20 mutation sites were positively correlated with cluster size, while 11 fatty acid mutation sites were negatively correlated with cluster size.

CONCLUSION: Our research results suggested that mutations in genes related to fatty acid metabolism were related to the transmission of M.tb. This research could help in the future control of the transmission of M.tb.

DOI: 10.1186/s12866-023-03072-9
PMCID: PMC10691062
PMID: 38041005 [Indexed for MEDLINE]

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

28. Addressing the needs of people with extensively drug-resistant TB through pre-approval access to drugs and research.

Public Health Action. 2023 Dec;13(4):126-129. doi: 10.5588/pha.23.0033. Epub 2023 Dec 7.

Stillo J(1)(2), Frick M(2)(3), Galarza J(2)(4), Kondratyuk S(2), Makone A(2)(5),

McKenna L(2)(3), Vandevelde W(2)(6), Winarni P(2), Agbassi P(2).

Multiple therapeutic options exist for people with drug-resistant TB (DR-TB), but there is an urgent need to improve access to novel compounds and regimens for people with difficult to treat forms of TB. In additional to formal research studies and clinical trials, other mechanisms of accessing promising new TB compounds need to be introduced as soon as these drugs have shown efficacy and safety in phase II trials. Pre-approval access programs for newer TB drugs such as bedaquiline, delamanid, and pretomanid all suffered from shortcomings. These can be addressed for the next generation of new TB drugs through a series of concerted actions by stakeholders at multiple levels. In this viewpoint, we advocate for transparent, accessible pre-approval access as a core element of person-centered care for DR-TB.

DOI: 10.5588/pha.23.0033
PMCID: PMC10703140
PMID: 38077718

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

29. Evolution and transmission of antibiotic resistance is driven by Beijing lineage Mycobacterium tuberculosis in Vietnam.

Microbiol Spectr. 2023 Dec 12;11(6):e0256223. doi: 10.1128/spectrum.02562-23. Epub 2023 Nov 16.

Silcocks M(#)(1), Chang X(#)(1)(2)(3), Thuong Thuong NT(#)(4)(5), Qin Y(6)(7), Minh Ha DT(8), Khac Thai PV(8), Vijay S(4)(5)(9), Anh Thu DD(4), Ngoc Ha VT(4), Ngoc Nhung H(4), Huu Lan N(8), Quynh Nhu NT(4), Edwards D(10), Nath A(6), Pham K(11), Duc Bang N(8), Hong Chau TT(4)(12), Thwaites G(4)(5), Heemskerk AD(13), Chuen Khor C(14), Teo YY(15), Inouye M(6)(16), Ong RT-H(15), Caws M(17)(18), Holt KE(#)(10)(19), Dunstan SJ(#)(1).

Drug-resistant tuberculosis (TB) infection is a growing and potent concern, and combating it will be necessary to achieve the WHO's goal of a 95% reduction in TB deaths by 2035. While prior studies have explored the evolution and spread of drug resistance, we still lack a clear understanding of the fitness costs (if any) imposed by resistance-conferring mutations and the role that Mtb genetic lineage plays in determining the likelihood of resistance evolution. This study offers insight into these questions by assessing the dynamics of resistance evolution in a high-burden Southeast Asian setting with a diverse lineage

composition. It demonstrates that there are clear lineage-specific differences in the dynamics of resistance acquisition and transmission and shows that different lineages evolve resistance via characteristic mutational pathways.

DOI: 10.1128/spectrum.02562-23
PMCID: PMC10714959
PMID: 37971428 [Indexed for MEDLINE]

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

30. Deep learning and radiomics of longitudinal CT scans for early prediction of tuberculosis treatment outcomes.

Eur J Radiol. 2023 Dec;169:111180. doi: 10.1016/j.ejrad.2023.111180. Epub 2023 Oct 30.

Nijiati M(1), Guo L(2), Abulizi A(1), Fan S(1), Wubuli A(3), Tuersun A(1), Nijiati P(1), Xia L(2), Hong K(2), Zou X(4).

BACKGROUND: To predict tuberculosis (TB) treatment outcomes at an early stage, prevent poor outcomes ofdrug-resistant tuberculosis(DR-TB) and interrupt transmission.

METHODS: An internal cohort for model development consists of 204 bacteriologically-confirmed TB patients who completed anti-tuberculosis treatment, with one pretreatment and two follow-up CT images (612 scans). Three radiomics feature-based models (RM) with multiple classifiers of Bagging, Random forest and Gradient boosting and two deep-learning-based models (i.e., supervised deep-learning model, SDLM; weakly supervised deep-learning model, WSDLM) are developed independently. Prediction scores of RM and deep-learning models with respectively highest performance are fused to create new fusion models under different fusion strategies. An additional independent validation was conducted on the external cohort comprising 80 patients (160 scans).

RESULTS: For RM scheme, 16 optimal radiomics features are finally selected using longitudinal scans. The AUCs of RM for Bagging, Random forest and Gradient boosting were 0.789, 0.773 and 0.764 in the internal cohort and 0.840, 0.834 and 0.816 in the external cohort, respectively. For deep learning-based scheme, AUCs of SDLM and WSDLM were 0.767 and 0.661 in the internal cohort, and 0.823 and 0.651 in the external. The fusion model yields AUCs from 0.767 to 0.802 in the internal cohort, and from 0.831 to 0.857 in the external cohort.

CONCLUSIONS: Fusion of radiomics features and deep-learning model may have the

potential to predict early failure outcome of DR-TB, which may be combined to help prevent poor TB treatment outcomes.

DOI: 10.1016/j.ejrad.2023.111180
PMID: 37949023 [Indexed for MEDLINE]

Conflict of interest statement: Declaration of Competing Interest The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: All authors have completed the ICMJE uniform disclosure form. L.G. Activities related to the present article: disclosed no relevant relationships. Activities not related to the present article: disclosed employee of Shenzhen Zhiying Medical Imaging. Other relationships: disclosed no relevant relationships. L.X. Activities related to the present article: disclosed no relevant relationships. Activities not related to the present article: disclosed employee of Shenzhen Zhiying Medical Imaging. K.H. Activities related to the present article: disclosed no relevant relationships. Activities not related to the present article: disclosed employee of Shenzhen Zhiying Medical Imaging. Other relationships: disclosed no relevant relationships. The other authors have no conflicts of interest to declare.

31. A potent subset of Mycobacterium tuberculosis glycoproteins as relevant candidates for vaccine and therapeutic target.

Sci Rep. 2023 Dec 14;13(1):22194. doi: 10.1038/s41598-023-49665-2.

Yari S(1), Afrough P(2), Yari F(3), Ghazanfari Jajin M(1), Fateh A(1), Hadizadeh Tasbiti A(4).

Tuberculosis (TB) remains one of the most afflictive bacterial infections globally. In high burden TB countries, surveillance, diagnosis and treatment of drug resistant TB (RR and X/MDRTB) display a crucial public health challenge. Therefore, we need new TB vaccines; diagnostic and therapeutic strategies to briskly prevent disease promotion; reduce drug-resistant TB and protect everyone from disease. The study identified various potent membrane and cell wall M. tuberculosis glycolipoproteins that are relevant for diagnostics, drug and vaccine discovery. A M. tuberculosis Proskauer and Beck broth culture was extracted for total proteins by ammonium sulfate method. After ConA-Affinity Chromatography reputed glycoproteins were collected followed by 2DE gel electrophoresis and LC Mass spectrometry. A total of 293 glycoproteins were identified using GlycoPP and IEDB database. Probable conserved trans-membrane protein (Rv0954), LpqN (Rv0583), PPE68 (Rv3873), Phosphate-binding protein

(Rv0932c), PPE61 (Rv3532) and LprA (Rv1270c), had the highest glycosylation percentage value with 13.86%, 11.84%, 11.68%, 11.1%, 10.59% and10.2%, respectively. Our study discloses several dominant glycoproteins that play roles in M. tuberculosis survival, and immunogenicity. These include glycoproteins involved in antigenicity, transport and biosynthesis of M. tuberculosis cell envelope, pathogen-host interaction and drug efflux pumps, which are considered as a feasible drug targets or TB new vaccine candidates.

DOI: 10.1038/s41598-023-49665-2
PMCID: PMC10719292
PMID: 38092899 [Indexed for MEDLINE]

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

32. Contezolid can replace linezolid in a novel combination with bedaquiline and pretomanid in a murine model of tuberculosis.

Antimicrob Agents Chemother. 2023 Dec 14;67(12):e0078923. doi: 10.1128/aac.00789-23. Epub 2023 Nov 15.

Almeida D(1), Li S-Y(1), Lee J(1), Hafkin B(2), Mdluli K(3), Fotouhi N(3), Nuermberger EL(1).

Contezolid is a new oxazolidinone with in vitro and in vivo activity against Mycobacterium tuberculosis comparable to that of linezolid. Pre-clinical and clinical safety studies suggest it may be less toxic than linezolid, making contezolid a potential candidate to replace linezolid in the treatment of drug-resistant tuberculosis. We evaluated the dose-ranging activity of contezolid, alone and in combination with bedaquiline and pretomanid, and compared it with linezolid at similar doses, in an established BALB/c mouse model of tuberculosis. Contezolid had an MIC of 1 µg/mL, similar to linezolid, and exhibited similar bactericidal activity in mice. Contezolid-resistant mutants selected in vitro had 32- to 64-fold increases in contezolid MIC and harbored mutations in the mce3R gene. These mutants did not display cross-resistance to linezolid. Our results indicate that contezolid has the potential to replace linezolid in regimens containing bedaquiline and pretomanid and likely other regimens.

DOI: 10.1128/aac.00789-23
PMCID: PMC10720489
PMID: 37966090 [Indexed for MEDLINE]

Conflict of interest statement: Barry Hafkin is an employee of MicuRx Pharmaceuticals, Khisimuzi Mdluli is an employee of the Bill & Melinda Gates Medical Research Institute, and Nader Fotouhi is an employee of the Global Alliance for Tuberculosis Drug Development.

33. In vitro antimycobacterial activity and interaction profiles of diarylthiourea-copper (II) complexes with antitubercular drugs against Mycobacterium tuberculosis isolates.

Tuberculosis (Edinb). 2023 Dec;143:102412. doi: 10.1016/j.tube.2023.102412. Epub 2023 Sep 25.

Bielenica A(1), Głogowska A(2), Augustynowicz-Kopeć E(2), Orzelska-Górka J(3), Kurpios-Piec D(4), Struga M(4).

The activity of several halogenated copper (II) complexes of 4-chloro-3-nitrophenylthiourea derivatives has been tested against Mycobacterium tuberculosis strains and strains of non-tuberculous mycobacteria. The compounds were 2-16 times more potent than current TB-drugs against multidrug-resistant M. tuberculosis 210. The 3,4-dichlorophenylthiourea complex (5) was equipotent to ethambutol (EMB) towards M. tuberculosis H37Rv and 192 strains. All derivatives acted 2-8 times stronger than isoniazid (INH) against nontuberculous isolates. In the presence of chosen coordinates, the 2-64 times reduction of MIC values of standard drugs was denoted. The synergistic interaction was found between the complex 4 and rifampicin (RMP), and additivity of 1-5, 8 in pairs with EMB and/or streptomycin (SM) against M. tuberculosis 800 was established. All coordination compounds in combination with at least one drug showed additive activity towards both H37Rv and 192 isolates. In 67% incidences of indifference, the individual MIC of a drug decreased 2-16-fold. One can conclude that the novel thiourea chelates described here are potent hits for further developments of new agents against tuberculosis.

DOI: 10.1016/j.tube.2023.102412
PMID: 37774599 [Indexed for MEDLINE]

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

34. Accuracy of the InnowaveDX MTB/RIF test for detection of Mycobacterium tuberculosis and rifampicin resistance: a prospective multicentre study.

Emerg Microbes Infect. 2023 Dec;12(1):2151382. doi: 10.1080/22221751.2022.2151382.

Deng Y(1), Ma Z(2), Su B(3), Bai G(4), Pan J(5), Wang Q(6), Cai L(7), Song Y(8), Shang Y(2), Ma P(3), Li J(4), Zhou Q(5), Mulati G(6), Fan D(7), Li S(2), Tan Y(3), Pang Y(2).

Early and accurate diagnosis of tuberculosis (TB) is necessary to initiate proper therapy for the benefit of the patients and to prevent disease transmission in the community. In this study, we developed the InnowaveDX MTB/RIF (InnowaveDX) to detect Mycobacterium tuberculosis (MTB) and rifampicin resistance simultaneously. A prospective multicentre study was conducted to evaluate the diagnostic performance of InnowaveDX for the detection MTB in sputum samples as compared with Xpert and culture. The calculated limit of detection (LOD) for InnowaveDX was 9.6 CFU/ml for TB detection and 374.9 CFU/ml for RIF susceptibility. None of the other bacteria tested produced signals that fulfilled the positive TB criteria, demonstrating a species-specificity of InnowaveDX. Then 951 individuals were enrolled at 7 hospitals, of which 607 were definite TB cases with positive culture and/or Xpert results, including 354 smear-positive and 253 smear-negative cases. InnowaveDX sensitivity was 92.7% versus bacteriologically TB standard. Further follow-up revealed that 61 (91.0%) out of 67 false-positive patients with no bacteriological evidence met the criteria of clinically diagnosed TB. Among 125 RIF-resistant TB patients diagnosed by Xpert, 108 cases were correctly identified by InnowaveDX, yielding a sensitivity of 86.4%. Additionally, the proportion of very low bacterial load in the discordant susceptibility group was significantly higher than in the concordant susceptibility group (P = 0.029). To conclude, we have developed a novel molecular diagnostic with promising detection capabilities of TB and RIF susceptibility. In addition, the discordant RIF susceptibility results between InnowaveDX and Xpert are more frequently observed in samples with very low bacterial load.

DOI: 10.1080/22221751.2022.2151382
PMCID: PMC9815255
PMID: 36416478 [Indexed for MEDLINE]

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

35. Multidrug-resistant tuberculous orchiepididymitis: a brief case report.

Rev Inst Med Trop Sao Paulo. 2023 Dec 4;65:e61. doi:

10.1590/S1678-9946202365061. eCollection 2023.

Souza CAT(1), Silva JSD(2), Correia AS(3), Rodrigues DS(1).

Tuberculosis (TB) is one of the leading causes of death by infectious diseases worldwide. Multidrug-resistant tuberculosis is a growing problem, especially in countries with high TB prevalence. Although the lungs are the organs most frequently affected by this disease, Mycobacterium tuberculosis can harm any organ, including the urogenital tract, causing extrapulmonary tuberculosis, which leads to a challenging diagnosis and consequent treatment delays. In this article, we present a case of orchiepididymitis caused by multidrug-resistant TB (MDR-TB) with a significantly delayed diagnosis, the proposed treatment according to the resistance profile, and the clinical outcomes.

DOI: 10.1590/S1678-9946202365061
PMCID: PMC10703499
PMID: 38055379 [Indexed for MEDLINE]

36. Quinoline Compounds Targeting the c-Ring of ATP Synthase Inhibit Drug-Resistant Pseudomonas aeruginosa.

ACS Infect Dis. 2023 Dec 8;9(12):2448-2456. doi: 10.1021/acsinfecdis.3c00317. Epub 2023 Nov 3.

Fraunfelter VM(1), Pugh BA(1), Williams APL(1), Ward KT(1), Jackson DO(1), Austin M(1), Ciprich JF(1), Dippy L(1), Dunford J(1), Edwards GN(1), Glass E(1), Handy KM(1), Kellogg CN(1), Llewellyn K(1), Nyberg KQ(1), Shepard SJ(1), Thomas C(1), Wolfe AL(1), Steed PR(1).

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Pseudomonas aeruginosa (PA) is a Gram-negative, biofilm-forming bacterium and an opportunistic pathogen. The growing drug resistance of PA is a serious threat that necessitates the discovery of novel antibiotics, ideally with previously underexplored mechanisms of action. Due to their central role in cell metabolism, bacterial bioenergetic processes are of increasing interest as drug targets, especially with the success of the ATP synthase inhibitor bedaquiline to treat drug-resistant tuberculosis. Like Mycobacterium tuberculosis, PA requires F1Fo ATP synthase for growth, even under anaerobic conditions, making

the PA ATP synthase an ideal drug target for the treatment of drug-resistant infection. In previous work, we conducted an initial screen for quinoline compounds that inhibit ATP synthesis activity in PA. In the present study, we report additional quinoline derivatives, including one with increased potency against PA ATP synthase in vitro and antibacterial activity against drug-resistant PA. Moreover, by expressing the PA ATP synthase in Escherichia coli, we show that mutations in the H+ binding site on the membrane-embedded rotor ring alter inhibition by the reported quinoline compounds. Identification of a potent inhibitor and its probable binding site on ATP synthase enables further development of promising quinoline derivatives into a viable treatment for drug-resistant PA infection.

DOI: 10.1021/acsinfecdis.3c00317
PMCID: PMC10714390
PMID: 37922420 [Indexed for MEDLINE]

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

37. Combination of MCL-1 and BCL-2 inhibitors is a promising approach for a host-directed therapy for tuberculosis.

Biomed Pharmacother. 2023 Dec;168:115738. doi: 10.1016/j.biopha.2023.115738. Epub 2023 Oct 19.

Arnett E(1), Pahari S(2), Leopold Wager CM(2), Hernandez E(2), Bonifacio JR(2), Lumbreras M(2), Renshaw C(2), Montoya MJ(2), Opferman JT(3), Schlesinger LS(4).

Tuberculosis (TB) accounts for 1.6 million deaths annually and over 25% of deaths due to antimicrobial resistance. Mycobacterium tuberculosis (M.tb) drives MCL-1 expression (family member of anti-apoptotic BCL-2 proteins) to limit apoptosis and grow intracellularly in human macrophages. The feasibility of re-purposing specific MCL-1 and BCL-2 inhibitors to limit M.tb growth, using inhibitors that are in clinical trials and FDA-approved for cancer treatment has not be tested previously. We show that specifically inhibiting MCL-1 and BCL-2 induces apoptosis of M.tb-infected macrophages, and markedly reduces M.tb growth in human and murine macrophages, and in a pre-clinical model of human granulomas. MCL-1 and BCL-2 inhibitors limit growth of drug resistant and susceptible M.tb in macrophages and act in additive fashion with the antibiotics isoniazid and rifampicin. This exciting work uncovers targeting the intrinsic apoptosis pathway as a promising approach for TB host-directed therapy. Since safety and activity studies are underway in cancer clinics for MCL-1 and BCL-2 inhibitors, we expect that re-purposing them for TB treatment should translate

more readily and rapidly to the clinic. Thus, the work supports further development of this host-directed therapy approach to augment current TB treatment.

DOI: 10.1016/j.biopha.2023.115738
PMID: 37864894 [Indexed for MEDLINE]

Conflict of interest statement: Declaration of Competing Interest The following patents have been submitted: Provisional patent number: 63/069,086, international patent number: PCT/US2021/047074.

38. GaMF1.39's antibiotic efficacy and its enhanced antitubercular activity in combination with clofazimine, Telacebec, ND-011992, or TBAJ-876.

Microbiol Spectr. 2023 Dec 12;11(6):e0228223. doi: 10.1128/spectrum.02282-23. Epub 2023 Nov 20.

Ragunathan P(1), Shuyi Ng P(2), Singh S(3), Poh WH(4), Litty D(5), Kalia NP(6), Larsson S(3), Harikishore A(1)(7), Rice SA(1)(4), Ingham PW(3), Müller V(5), Moraski G(8), Miller MJ(9), Dick T(10)(11)(12), Pethe K(1)(3)(13), Grüber G(1).

New drugs are needed to combat multidrug-resistant tuberculosis. The electron transport chain (ETC) maintains the electrochemical potential across the cytoplasmic membrane and allows the production of ATP, the energy currency of any living cell. The mycobacterial engine F-ATP synthase catalyzes the formation of ATP and has come into focus as an attractive and rich drug target. Recent deep insights into these mycobacterial F1FO-ATP synthase elements opened the door for a renaissance of structure-based target identification and inhibitor design. In this study, we present the GaMF1.39 antimycobacterial compound, targeting the rotary subunit γ of the biological engine. The compound is bactericidal, inhibits infection ex vivo, and displays enhanced anti-tuberculosis activity in combination with ETC inhibitors, which promises new strategies to shorten tuberculosis chemotherapy.

DOI: 10.1128/spectrum.02282-23
PMCID: PMC10715162
PMID: 37982630 [Indexed for MEDLINE]

Conflict of interest statement: G.G. and P.S.N. are inventors on the patent 10201911205R, which is related to the inhibitor described in this article.

39. Serial electrocardiogram recordings revealed a high prevalence of QT interval prolongation in patients with tuberculosis receiving fluoroquinolones.

J Formos Med Assoc. 2023 Dec;122(12):1255-1264. doi: 10.1016/j.jfma.2023.05.020. Epub 2023 May 31.

Ju KS(1), Lee RG(2), Lin HC(3), Chen JH(4), Hsu BF(3), Wang JY(5), Van Dong N(6), Yu MC(7), Lee CH(8).

BACKGROUND: Fluoroquinolones, crucial components of treatment regimens for drug-resistant tuberculosis (TB), are associated with QT interval prolongation and risks of fatal cardiac arrhythmias. However, few studies have explored dynamic changes in the QT interval in patients receiving QT-prolonging agents.

METHODS: This prospective cohort study recruited hospitalized patients with TB who received fluoroquinolones. The study investigated the variability of the QT interval by using serial electrocardiograms (ECGs) recorded four times daily. This study analyzed the accuracy of intermittent and single-lead ECG monitoring in detecting QT interval prolongation.

RESULTS: This study included 32 patients. The mean age was 68.6 ± 13.2 years. The results revealed mild-to-moderate and severe QT interval prolongation in 13 (41%) and 5 (16%) patients, respectively. The incremental yields in sensitivity of one to four daily ECG recordings were 61.0%, 26.1%, 5.6%, and 7.3% in detecting mild-to-moderate QT interval prolongation, and 66.7%, 20.0%, 6.7%, and 6.7% in detecting severe QT interval prolongation. The sensitivity levels of lead II and V5 ECGs in detecting mild-to-moderate and severe QT interval prolongation exceeded 80%, and their specificity levels exceeded 95%.

CONCLUSION: This study revealed a high prevalence of QT interval prolongation in older patients with TB who receive fluoroquinolones, particularly those with multiple cardiovascular risk factors. Sparsely intermittent ECG monitoring, the prevailing strategy in active drug safety monitoring programs, is inadequate owing to multifactorial and circadian QT interval variability. Additional studies performing serial ECG monitoring are warranted to enhance the understanding of dynamic QT interval changes in patients receiving QT-prolonging anti-TB agents.

DOI: 10.1016/j.jfma.2023.05.020

PMID: 37268474 [Indexed for MEDLINE]

Conflict of interest statement: Declaration of competing interest The authors have no conflicts of interest relevant to this article.

40. Mistaken identity: Reporting two cases of rare forms of extrapulmonary tuberculosis in Solomon Islands.

Int J Surg Case Rep. 2023 Dec 10;114:109141. doi: 10.1016/j.ijscr.2023.109141. Online ahead of print.

Bush D(1), Fiuramo F(2), Liligeto J(2), Ipulu L(2), Diau J(2), Jagilly R(2).

INTRODUCTION AND IMPORTANCE: Extrapulmonary tuberculosis (EPTB) is a relatively rare and difficult-to-diagnose manifestation of Myobacterium tuberculosis (TB) infection.

CASE PRESENTATION: This study reports the cases of a 47-year-old male and a 35-year old female with rare forms of EPTB who sought medical care in Solomon Islands. Both patients presented with nondescript symptoms and a chief complaint of pain. Initial diagnosis for the male and female patient was an abacterial colon polypoid mass and a urinary tract infection (UTI) respectively. Following unsuccessful treatment for UTI and further investigation, the surgical team diagnosed the female patient with a tuberculosis spondylitis and a bilateral psoas abscess. The male patient was subsequently diagnosed with isolated colonic tuberculosis. After starting medication, the patients were discharged and prescribed 9-month treatment regimens. During outpatient treatment both patients reported suboptimal adherence. The female patient resumed treatment and showed improvement while the male patient discontinued treatment, experienced worsening symptoms, and ultimately died.

CLINICAL DISCUSSION: The nonspecific symptoms of extrapulmonary TB infection make it difficult to diagnose. Cases of rare forms of EPTB are particularly challenging to identify. Misdiagnosis may further increase the likelihood of mortality and morbidity in these cases. Intensive medication counseling, patient outreach, and regularly scheduled follow-up visits may reduce the incidence of poor adherence and reduce the risk of developing drug-resistant TB.

CONCLUSION: Medical practitioners in tuberculosis-endemic countries like Solomon Islands should maintain a high clinical index of suspicion in diagnosing EPTB. Future research should investigate the prevalence of TB and EPTB in the Solomon Islands.

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PMCID: PMC10726230
PMID: 38086130

Conflict of interest statement: Declaration of competing interest The authors report no declaration of competing interest.

41. A precision overview of genomic resistance screening in Ecuadorian isolates of Mycobacterium tuberculosis using web-based bioinformatics tools.

PLoS One. 2023 Dec 5;18(12):e0294670. doi: 10.1371/journal.pone.0294670. eCollection 2023.

Morey-León G(1)(2)(3), Mejía-Ponce PM(4), Granda Pardo JC(5), Muñoz-Mawyin K(6), Fernández-Cadena JC(7), García-Moreira E(8), Andrade-Molina D(1)(6), Licona-Cassani C(4), Berná L(9)(10).

INTRODUCTION: Tuberculosis (TB) is among the deadliest diseases worldwide, and its impact is mainly due to the continuous emergence of resistant isolates during treatment due to the laborious process of resistance diagnosis, nonadherence to treatment and circulation of previously resistant isolates of Mycobacterium tuberculosis. In this study, we evaluated the performance and functionalities of web-based tools, including Mykrobe, TB-profiler, PhyResSE, KvarQ, and SAM-TB, for detecting resistance in 88 Ecuadorian isolates of Mycobacterium tuberculosis drug susceptibility tested previously. Statistical analysis was used to determine the correlation between genomic and phenotypic analysis. Our results showed that with the exception of KvarQ, all tools had the highest correlation with the conventional drug susceptibility test (DST) for global resistance detection (98% agreement and 0.941 Cohen's kappa), while SAM-TB, PhyResSE, TB-profiler and Mykrobe had better correlations with DST for first-line drug analysis individually. We also identified that in our study, only 50% of mutations characterized by the web-based tools in the rpoB, katG, embB, pncA, gyrA and rrs regions were canonical and included in the World Health Organization (WHO) catalogue. Our findings suggest that SAM-TB, PhyResSE, TB-profiler and Mykrobe were efficient in determining canonical resistance-related mutations, but more analysis is needed to improve second-line detection. Improving surveillance programs using whole-genome sequencing tools for first-line drugs, MDR-TB and XDR-TB is essential to understand the molecular epidemiology of TB in Ecuador.

IMPORTANCE: Tuberculosis, an infectious disease caused by Mycobacterium

tuberculosis, most commonly affects the lungs and is often spread through the air when infected people cough, sneeze, or spit. However, despite the existence of effective drug treatment, patient adherence, long duration of treatment, and late diagnosis have reduced the effectiveness of therapy and increased drug resistance. The increase in resistant cases, added to the impact of the COVID-19 pandemic, has highlighted the importance of implementing efficient and timely diagnostic methodologies worldwide. The significance of our research is in evaluating and identifying a more efficient and user-friendly web-based tool to characterize resistance in Mycobacterium tuberculosis by whole-genome sequencing, which will allow more routine application to improve TB strain surveillance programs locally.

DOI: 10.1371/journal.pone.0294670
PMCID: PMC10697571
PMID: 38051742 [Indexed for MEDLINE]

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

42. Universal drug-susceptibility testing of first-line drugs to preserve their efficacy: An essential strategy to defeat tuberculosis.

J Clin Tuberc Other Mycobact Dis. 2023 Aug 22;33:100394. doi: 10.1016/j.jctube.2023.100394. eCollection 2023 Dec.

Dev Bhattarai M(1).

DOI: 10.1016/j.jctube.2023.100394
PMCID: PMC10475499
PMID: 37671085

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.

43. Clustering minimal inhibitory concentration data through Bayesian mixture models: An application to detect Mycobacterium tuberculosis resistance

mutations.

Stat Methods Med Res. 2023 Dec;32(12):2423-2439. doi: 10.1177/09622802231211010. Epub 2023 Nov 3.

Grazian C(1)(2).

Antimicrobial resistance is becoming a major threat to public health throughout the world. Researchers are attempting to contrast it by developing both new antibiotics and patient-specific treatments. In the second case, whole-genome sequencing has had a huge impact in two ways: first, it is becoming cheaper and faster to perform whole-genome sequencing, and this makes it competitive with respect to standard phenotypic tests; second, it is possible to statistically associate the phenotypic patterns of resistance to specific mutations in the genome. Therefore, it is now possible to develop catalogues of genomic variants associated with resistance to specific antibiotics, in order to improve prediction of resistance and suggest treatments. It is essential to have robust methods for identifying mutations associated to resistance and continuously updating the available catalogues. This work proposes a general method to study minimal inhibitory concentration distributions and to identify clusters of strains showing different levels of resistance to antimicrobials. Once the clusters are identified and strains allocated to each of them, it is possible to perform regression method to identify with high statistical power the mutations associated with resistance. The method is applied to a new 96-well microtiter plate used for testing Mycobacterium tuberculosis.

DOI: 10.1177/09622802231211010
PMCID: PMC10710010
PMID: 37920984 [Indexed for MEDLINE]

Conflict of interest statement: Declaration of conflicting interestsThe author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

44. Linezolid does not improve bactericidal activity of rifampin-containing first-line regimens in animal models of TB meningitis.

Int J Antimicrob Agents. 2023 Dec 5:107048. doi: 10.1016/j.ijantimicag.2023.107048. Online ahead of print.

Tucker EW(1), Ruiz-Bedoya CA(2), Mota F(2), Erice C(1), Kim J(1), de Jesus P(2), Jahdav R(3), Bahr M(2), Flavahan K(2), Chen X(2), Peloquin CA(4), Freundlich JS(3), Jain SK(5).

Tuberculous meningitis (TB meningitis) is the most devastating form of tuberculosis (TB) and there is a critical need to optimize treatment. Linezolid is approved for multidrug resistant TB and has shown encouraging results in retrospective TB meningitis studies, with several clinical trials underway assessing its additive effects on high-dose (35 mg/kg/day) or standard-dose (10 mg/kg/day) rifampin-containing regimens. However, the efficacy of adjunctive linezolid to rifampin-containing first-line TB meningitis regimens and the tissue pharmacokinetics (PK) in the central nervous system (CNS) are not known. We therefore conducted cross-species studies in two mammalian (rabbits and mice) models of TB meningitis to test the efficacy of linezolid when added to the first-line TB regimen and measure detailed tissue PK (multicompartmental positron emission tomography [PET] imaging and mass spectrometry). Addition of linezolid did not improve the bactericidal activity of the high-dose rifampin-containing regimen in either animal model. Moreover, the addition of linezolid to standard-dose rifampin in mice also did not improve its efficacy. Linezolid penetration (tissue/plasma) into the CNS was compartmentalized with lower than previously reported brain and cerebrospinal fluid (CSF) penetration, which decreased further two weeks after initiation of treatment. These results provide important data regarding the addition of linezolid for the treatment of TB meningitis.

DOI: 10.1016/j.ijantimicag.2023.107048
PMID: 38061419

Pub Med Non-Open Access

45. Micro-nanoemulsion and nanoparticle-assisted drug delivery against drug-resistant tuberculosis: recent developments.

Clin Microbiol Rev. 2023 Dec 20;36(4):e0008823. doi: 10.1128/cmr.00088-23. Epub 2023 Nov 30.

Suman SK(1), Chandrasekaran N(2), Priya Doss CG(3).

SUMMARYTuberculosis (TB) is a major global health problem and the second most prevalent infectious killer after COVID-19. It is caused by Mycobacterium tuberculosis (Mtb) and has become increasingly challenging to treat due to drug resistance. The World Health Organization declared TB a global health emergency in 1993. Drug resistance in TB is driven by mutations in the bacterial genome that can be influenced by prolonged drug exposure and poor patient adherence.

The development of drug-resistant forms of TB, such as multidrug resistant, extensively drug resistant, and totally drug resistant, poses significant therapeutic challenges. Researchers are exploring new drugs and novel drug delivery systems, such as nanotechnology-based therapies, to combat drug resistance. Nanodrug delivery offers targeted and precise drug delivery, improves treatment efficacy, and reduces adverse effects. Along with nanoscale drug delivery, a new generation of antibiotics with potent therapeutic efficacy, drug repurposing, and new treatment regimens (combinations) that can tackle the problem of drug resistance in a shorter duration could be promising therapies in clinical settings. However, the clinical translation of nanomedicines faces challenges such as safety, large-scale production, regulatory frameworks, and intellectual property issues. In this review, we present the current status, most recent findings, challenges, and limiting barriers to the use of emulsions and nanoparticles against drug-resistant TB.

DOI: 10.1128/cmr.00088-23
PMID: 38032192

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

46. Tuberculosis Preventive Treatment.

Indian J Pediatr. 2023 Dec 14. doi: 10.1007/s12098-023-04969-z. Online ahead of print.

Tayal A(1), Kabra SK(2).

Some individuals exposed to Mycobacterium tuberculosis develop a latent infection and remain at a lifelong risk of developing tuberculosis (TB) disease, a state called as TB infection (TBI). TB preventive treatment (TPT) aims to treat TBI and prevent progression to active TB in an exposed or infected person. Currently, it is not possible to confirm TBI microbiologically, but can be identified indirectly by means of immune-based tests [Tuberculin skin test (TST), interferon-gamma release assays (IGRAs)]. It is crucial to rule out active TB before initiating TPT. TPT regimens have evolved with time. The most widely used regimen is 6 mo of daily Isoniazid (INH) (6H). Another regime in pipeline for persons >2 y, but not yet widely available, is 3HP (3 mo of weekly Isoniazid and Rifapentine). TPT to contacts of drug resistant TB (DR-TB) patients needs to be tailored depending on the resistance pattern in the index case, and relies on a bacteriological confirmation of the same. Individuals receiving TPT should be closely monitored for emergence of any signs or symptoms suggestive of active TB disease while on TPT.

DOI: 10.1007/s12098-023-04969-z
PMID: 38095783

47. Multi-drug-resistant tuberculosis and its associated factors among pulmonary tuberculosis patients linked to first-line anti-tuberculosis drugs in north-west Ethiopia.

J Med Microbiol. 2023 Dec;72(12). doi: 10.1099/jmm.0.001775.

Erkihun M(1), Kiros T(1), Berhan A(1), Ayele B(2).

Introduction. Multi-drug-resistant tuberculosis (MDR-TB) is an emerging global challenge. Ethiopia is one of the 20 top countries with the highest estimated numbers of incidents of MDR-TB. Recently, the World Health Organization warned that drug-resistant TB is escalating and called for concerted action to reduce the spread of drug resistance.

Hypothesis. The current study investigated MDR-TB in patients receiving first-line anti-TB drug treatment and associated factors.

Aim. The study aimed to determine the prevalence of MDR-TB and its associated factors among smear-positive pulmonary TB patients receiving first-line anti-TB drug treatment.

Methodology. An institution-based cross-sectional study was employed. All data were collected from laboratory result log books and information via a questionnaire. Samples from 205 smear-positive pulmonary TB patients were selected among first-line drug treatment by a systematic sampling method. Specimens were transported to Felege Hiwot referral hospital laboratory for GeneXpert testing. Factors associated with an outcome variable in binary multi-variable logistic regression analysis at P<0.05 were considered statistically significant variables. An ethical approval letter was taken to the respective health facility and written consent was obtained from each participant.

Results. The overall prevalence of MDR-TB was 9.3 % (95 % CI, 5.4 13.7 %). Sign and symptom experience of anti-TB drug side effects [adjusted odds ratio (AOR)=0.18, 95 % CI=0.03-0.99, P=0.049] and co-morbidity (AOR=0.03, 95 % CI=0.01-0.55, P=0.02) were statistically associated with the development of MDR-TB infection

Conclusion. The prevalence of MDR-TB was

high (9.3%) and contributed highly to new cases (8.3%). Factors associated with MDR-TB were previous treatment, co-morbidity and laboratory diagnosis method prior to TB treatment. Therefore, this finding aims to maximize early detection and treatment, strengthening TB infection control, and proper implementation of directly observed therapy short course recommendations to reduce the burden of MDR-TB.

DOI: 10.1099/jmm.0.001775
PMID: 38099651 [Indexed for MEDLINE]

48. Revolutionizing Tuberculosis Treatment: Uncovering New Drugs and Breakthrough Inhibitors to Combat Drug-Resistant Mycobacterium tuberculosis.

ACS Infect Dis. 2023 Dec 8;9(12):2369-2385. doi: 10.1021/acsinfecdis.3c00436. Epub 2023 Nov 9.

Verma A(1), Naik B(2), Kumar V(1), Mishra S(3), Choudhary M(1), Khan JM(4), Gupta AK(2), Pandey P(5), Rustagi S(6), Kakati B(7), Gupta S(1).

Tuberculosis (TB) is a global health threat that causes significant mortality. This review explores chemotherapeutics that target essential processes in Mycobacterium tuberculosis, such as DNA replication, protein synthesis, cell wall formation, energy metabolism, and proteolysis. We emphasize the need for new drugs to treat drug-resistant strains and shorten the treatment duration. Emerging targets and promising inhibitors were identified by examining the intricate biology of TB. This review provides an overview of recent developments in the search for anti-TB drugs with a focus on newly validated targets and inhibitors. We aimed to contribute to efforts to combat TB and improve therapeutic outcomes.

DOI: 10.1021/acsinfecdis.3c00436
PMID: 37944023 [Indexed for MEDLINE]

49. Repurposing Azoles to Resolve Serotogenic Toxicity Associated with Linezolid to Combat Multidrug-Resistant Tuberculosis.

ACS Med Chem Lett. 2023 Nov 1;14(12):1754-1759. doi: 10.1021/acsmedchemlett.3c00406. eCollection 2023 Dec 14.

Girase RT(1), Ahmad I(1), Oh JM(2), Kim H(2), Mathew B(3), Vagolu SK(4), Tønjum T(4)(5), Desai NC(6), Sriram D(7), Kumari J(7), Patel HM(1).

Serotogenic toxicity is a major hurdle associated with Linezolid in the treatment of drug-resistant tuberculosis (TB) due to the inhibition of monoamine

oxidase (MAO) enzymes. Azole compounds demonstrate structural similarities to the recognized anti-TB drug Linezolid, making them intriguing candidates for repurposing. Therefore, we have repurposed azoles (Posaconazole, Itraconazole, Miconazole, and Clotrimazole) for the treatment of drug-resistant TB with the anticipation of their selectivity in sparing the MAO enzyme. The results of repurposing revealed that Clotrimazole showed equipotent activity against the Mycobacterium tuberculosis (Mtb) H37Rv strain compared to Linezolid, with a minimal inhibitory concentration (MIC) of 2.26 μM. Additionally, Clotrimazole exhibited reasonable MIC50 values of 0.17 μM, 1.72 μM, 1.53 μM, and 5.07 μM against the inhA promoter+, katG+, rpoB+, and MDR clinical Mtb isolates, respectively, compared to Linezolid. Clotrimazole also exhibited 3.90-fold less inhibition of MAO-A and 50.35-fold less inhibition of MAO-B compared to Linezolid, suggesting a reduced serotonergic toxicity burden.

DOI: 10.1021/acsmedchemlett.3c00406
PMCID: PMC10726462
PMID: 38116435

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

50. Treatment outcome, recurrence and safety of multidrug-resistant TB treated with low-dose linezolid.

Int J Tuberc Lung Dis. 2023 Dec 1;27(12):918-924. doi: 10.5588/ijtld.23.0068.

Chung C(1), Jo KW(2), Shim TS(2).

BACKGROUND: Linezolid (LZD) is a key treatment option for patients with multidrug-resistant/rifampicin-resistant TB (MDR/RR-TB). We investigated the long-term treatment outcomes and safety of MDR/RR-TB treatment using low-dose LZD.METHODS: Medical records of patients with MDR/RR-TB treated with LZD ≥4 weeks between 2004 and 2018 at the Asan Medical Center, Seoul, Republic of Korea, were reviewed. Standard-dose and low-dose LZD groups were defined as patients initially administered LZD ≥600 mg/day or 300 mg/day, respectively.RESULTS: Among 94 patients, 65 were included in the low-dose LZD group; mean age was 43.1 ± 15.6 years, 53 (56.4%) were men and 77 (83.7%) were resistant to fluoroquinolone. The low-dose LZD group showed features of less severe disease, such as limited MDR-TB history and less severe radiological findings. There was no difference in treatment outcomes, relapse and safety between groups. In the low-dose LZD group, 54 (83.1%) succeeded treatment, of whom 48 (88.9%) were followed-up for a median of 38 months; there was no

recurrence. Adverse drug reactions were reported in 41 (63.1%); peripheral neuropathy was most frequently reported (n = 31, 47.7%), while myelosuppression was reported in 12 (18.5%).CONCLUSION: Low-dose LZD in selected patients with less severe disease is both effective in the long-term and safe for the treatment of MDR/RR-TB.

DOI: 10.5588/ijtld.23.0068
PMID: 38042970 [Indexed for MEDLINE]

51. Pre-extensively drug-resistant and extensively drug-resistant tuberculosis in Latin America and the Caribbean: A systematic review and meta-analysis.

Am J Infect Control. 2023 Dec 5:S0196-6553(23)00822-2. doi: 10.1016/j.ajic.2023.12.001. Online ahead of print.

Alarcon-Braga EA(1), Salazar-Valdivia FE(1), Estrada-Grossmann JM(1), Mendez-Guerra C(1), Pacheco-Barrios N(2), Al-Kassab-Córdova A(3).

BACKGROUND: The growing threat from pre-extensively drug resistant tuberculosis (pre-XDR-TB) and extensively drug resistant tuberculosis (XDR-TB) poses a major public health concern in Latin America and the Caribbean (LAC). Therefore, this study aimed to summarize the available evidence on the prevalence of pre-XDR-TB and XDR-TB among patients with multidrug-resistant tuberculosis (MDR-TB) in LAC.

METHODS: A systematic review was conducted in the following databases on June 3, 2023: PubMed, Scopus, Ovid Medline, Web of Science, Scielo and LILACS. We estimated pooled proportions using a random effects model (Dersimonian and Laird). The 95% confidence intervals (95% CI) were calculated using the binomial exact method (Clopper-Pearson Method). Subgroup (by time period and country) and sensitivity analyses were performed.

RESULTS: Twenty-nine studies were eligible for the qualitative synthesis and 27 for meta-analysis (n = 15,565). The pooled prevalence of XDR-TB in the study participants was 5% (95% CI: 3%-6%), while that of pre-XDR-TB was 10% (95% CI 7%-14%). Cuba (6%, 95% CI 0%-17%) and Peru (6%, 95% CI 5%-7%) had the highest pooled prevalence of XDR-TB. Regarding pre-XDR-TB, Brazil (16%, 95% CI 11%-22%) and Peru (13%, 95% CI: 9%-16%) showed a higher prevalence.

CONCLUSION: The pooled prevalence of pre-XDR-TB and XDR-TB in LAC was 10% and 5%, respectively. Governments should strengthen drug resistance surveillance and TB programs.

DOI: 10.1016/j.ajic.2023.12.001
PMID: 38061402

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

52. Arylidene and amino spacer-linked rhodanine-quinoline hybrids as upgraded antimicrobial agents.

Chem Biol Drug Des. 2023 Dec;102(6):1632-1642. doi: 10.1111/cbdd.14345. Epub 2023 Sep 12.

Khalifa Z(1), Upadhyay R(1), Patel AB(1).

Antibiotic resistance associated with various microorganisms such as Gram-positive, Gram-negative, fungal strains, and multidrug-resistant tuberculosis increases the risk of healthcare survival. Preliminary therapeutics becoming ineffective that might lead to noteworthy mortality presents a crucial challenge for the scientific community. Hence, there is an urgent need to develop hybrid compounds as antimicrobial agents by combining two or more bioactive heterocyclic moieties into a single molecular framework with fewer side effects and a unique mode of action. This review highlights the recent advances (2013-2023) in the pharmacology of rhodanine-linked quinoline hybrids as more effective antimicrobial agents. In the drug development process, linker hybrids acquire the top position due to their excellent π-stacking and Van der Waals interaction with the DNA active sites of pathogens. A molecular hybridization strategy has been optimized, indicating that combining these two bioactive moieties with an arylidene and an amino spacer linker increases the antimicrobial potential and reduces drug resistance. Moreover, the structure-activity relationship study is discussed to express the role of various functional groups in improving and decrementing antimicrobial activities for rational drug design. Also, a linker approach may accelerate the development of dynamic antimicrobial agents through molecular hybridization.

DOI: 10.1111/cbdd.14345
PMID: 37697906 [Indexed for MEDLINE]

53. Meropenem-vaborbactam restoration of first-line drug efficacy and comparison of meropenem-vaborbactam-moxifloxacin versus BPaL MDR-TB regimen.

Int J Antimicrob Agents. 2023 Dec;62(6):106968. doi: 10.1016/j.ijantimicag.2023.106968. Epub 2023 Sep 17.

Singh S(1), Gumbo T(2), Alffenaar JW(3), Boorgula GD(1), Shankar P(1), Thomas TA(4), Dheda K(5), Malinga L(6), Raj P(7), Aryal S(8), Srivastava S(9).

BACKGROUND: Meropenem in combination with β-lactamase inhibitors (BLIs) and other drugs was tested to identify alternative treatment regimens for multidrug-resistant tuberculosis (MDR-TB).

METHODS: The following were performed: (1) MIC experiments; (2) static time-kill studies (STKs) with different BLIs; and (3) a hollow fibre model system of TB (HFS-TB) studies with meropenem-vaborbactam combined with human equivalent daily doses of 20 mg/kg or 35 mg/kg rifampin, or moxifloxacin 400 mg, or linezolid 600 mg vs. bedaquiline-pretonamid-linezolid (BPaL) for MDR-TB. The studies were performed using Mycobacterium tuberculosis (M. tuberculosis) H37Rv and an MDR-TB clinical strain (named M. tuberculosis 16D) that underwent whole genome sequencing. Exponential decline models were used to calculate the kill rate constant (K) of different HFS-TB regimens.

RESULTS: Whole genome sequencing revealed mutations associated with resistance to rifampin, isoniazid, and cephalosporins. The meropenem-vaborbactam MIC of M. tuberculosis was H37Rv 2 mg/L and > 128 mg/L for M. tuberculosis 16D. Relebactam and vaborbactam improved both the potency and efficacy of meropenem in STKs. Meropenem-vaborbactam alone failed to kill M. tuberculosis 16D but killed below day 0 burden when combined with isoniazid and rifampin, with the moxifloxacin combination being the most effective and outranking bedaquiline and pretomanid. In the HFS-TB, meropenem-vaborbactam-moxifloxacin and BPaL had the highest K (log10 cfu/mL/day) of 0.31 (95% CI 0.17-0.58) and 0.34 (95% CI 0.21-0.56), while meropenem-vaborbactam-rifampin (35 mg/kg) had a K of 0.18 (95% CI 0.12-0.25). The K for meropenem-vaborbactam-moxifloxacin-linezolid demonstrated antagonism.

CONCLUSION: Adding meropenem-vaborbactam could potentially restore the efficacy of isoniazid and rifampin against MDR-TB. The meropenem-vaborbactam-moxifloxacin backbone regimen has implications for creating a new effective MDR-TB regimen.

DOI: 10.1016/j.ijantimicag.2023.106968
PMID: 37726063 [Indexed for MEDLINE]

54. Baseline and treatment-emergent bedaquiline resistance in drug-resistant tuberculosis: a systematic review and meta-analysis.

Eur Respir J. 2023 Dec 14;62(6):2300639. doi: 10.1183/13993003.00639-2023. Print

2023 Dec.

Perumal R(1)(2)(3), Bionghi N(4)(3), Nimmo C(5), Letsoalo M(6), Cummings MJ(7), Hopson M(4), Wolf A(7), Jubaer SA(8), Padayatchi N(6), Naidoo K(6), Larsen MH(8)(3), O'Donnell M(6)(7)(9)(3).

DOI: 10.1183/13993003.00639-2023
PMID: 37945030 [Indexed for MEDLINE]

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

55. Tuberculosis multirresistente en Colombia, 2013-2018: estudio de casos y controles.

Biomedica. 2023 Dec 1;43(4):447-456. doi: 10.7705/biomedica.6842.

[Article in English, Spanish; Abstract available in Spanish from the publisher]

Puerto GM(1), Castro CM(2), Rubio VV(3), Fadul S(4), Montes F(5).

INTRODUCTION: Multidrug-resistant/rifampicin-resistant tuberculosis (MDR/RR-TB) is difficult to control, has high morbidity and mortality, and demands priority public health intervention. In Colombia, MDR/RR-TB has been becoming more widespread annually. Before the COVID-19 pandemic, over an 8-year period, the number of cases of multidrug-resistant tuberculosis in Colombia was close to a thousand cases. Timely identification of the different risk factors for MDR/RR-TB will contribute fundamentally to the systematic management.
OBJECTIVE: To determine which risk factors were associated with the presentation of MDR in Colombia between 2013 and 2018.

MATERIALS AND METHODS: A retrospective case-control study was carried out, for which the data from the routine surveillance of MDR/events in the country were used.

RESULTS: The cases of multidrug-resistant tuberculosis were mainly in young people, Afrodescendants, and males. Of the clinical conditions, comorbidities such as malnutrition, diabetes, and HIV, presence of at least one factor, such as drug dependence, taking immunosuppressive medications, belonging to the black race, afro, and living in an area of high disease burden were risk factors.

CONCLUSION: In addition to the diagnosis and timely provision of MDR-TB treatment, it is necessary that public health programs at the local level pay special attention to patients with the identified risk factors.

DOI: 10.7705/biomedica.6842
PMID: 38109144 [Indexed for MEDLINE]

56. Protein binding investigation of first-line and second-line antituberculosis drugs.

Int J Antimicrob Agents. 2023 Dec;62(6):106999. doi: 10.1016/j.ijantimicag.2023.106999. Epub 2023 Oct 13.

Fage D(1), Aalhoul F(2), Cotton F(3).

Data on protein binding are incomplete for first-line antituberculosis drugs, and lacking for second-line antituberculosis drugs that are used extensively for multi-drug-resistant tuberculosis (levofloxacin, linezolid and moxifloxacin). Thus, the main purposes of this study were to investigate: (i) the relationship between carrier protein concentration and drug binding; and (ii) the feasibility of predicting free drug concentration using in-vitro and in-vivo results. In-vitro experiments were performed on spiked plasma mimicking real-case samples (drug combinations from clinical practice). Median in-vivo protein binding was 1.5% for ethambutol, 9.7% for isoniazid, 0.7% for pyrazinamide and 88.2% for rifampicin; and median in-vitro protein binding was 26.2% for levofloxacin, 12.8% for linezolid and 46.3% for moxifloxacin. Albumin concentration (<30 g/L) had a moderate impact on moxifloxacin binding and a strong impact on levofloxacin, linezolid and rifampicin binding. Determination of the free drug concentration seems to be of little value for ethambutol, isoniazid, moxifloxacin and pyrazinamide; limited value for linezolid because of its low binding; and major value for rifampicin in hypoalbuminaemic patients with tuberculosis, and levofloxacin because total concentration was an inaccurate reflection of free concentration. The free concentration predicted by the mathematical model was suitable for levofloxacin and linezolid, whereas the real free concentration should be measured for rifampicin. Further investigations should be carried out to investigate the benefit of using free concentration for levofloxacin, linezolid and rifampicin, particularly in the critical period of active tuberculosis associated with hypoalbuminaemia.

DOI: 10.1016/j.ijantimicag.2023.106999
PMID: 37838149 [Indexed for MEDLINE]

57. Nano vs Resistant Tuberculosis: Taking the Lung Route.

AAPS PharmSciTech. 2023 Dec 4;24(8):252. doi: 10.1208/s12249-023-02708-3.

Sharma D(1), Pooja(1), Nirban S(1), Ojha S(2), Kumar T(1), Jain N(3), Mohamad N(4), Kumar P(5), Pandey M(6).

Tuberculosis (TB) is among the top 10 infectious diseases worldwide. It is categorized among the leading killer diseases that are the reason for the death of millions of people globally. Although a standardized treatment regimen is available, non-adherence to treatment has increased multi-drug resistance (MDR) and extensive drug-resistant (XDR) TB development. Another challenge is targeting the death of TB reservoirs in the alveoli via conventional treatment. TB Drug resistance may emerge as a futuristic restraint of TB with the scarcity of effective Anti-tubercular drugs. The paradigm change towards nano-targeted drug delivery systems is mostly due to the absence of effective therapy and increased TB infection recurrent episodes with MDR. The emerging field of nanotechnology gave an admirable opportunity to combat MDR and XDR via accurate diagnosis with effective treatment. The new strategies targeting the lung via the pulmonary route may overcome the new incidence of MDR and enhance patient compliance. Therefore, this review highlights the importance and recent research on pulmonary drug delivery with nanotechnology along with prevalence, the need for the development of nanotechnology, beneficial aspects of nanomedicine, safety concerns of nanocarriers, and clinical studies.

DOI: 10.1208/s12249-023-02708-3
PMID: 38049695 [Indexed for MEDLINE]

58. Impact of Mycobacterium tuberculosis strain type on multidrug-resistant tuberculosis severity, Republic of Moldova.

J Infect. 2023 Dec;87(6):588-591. doi: 10.1016/j.jinf.2023.10.001. Epub 2023 Oct 10.

Chesov E(1), Chesov D(2), Reimann M(3), Dreyer V(4), Utpatel C(4), Gröschel MI(5), Ciobanu N(6), Crudu V(6), Lange C(7), Heyckendorf J(8), Merker M(9).

DOI: 10.1016/j.jinf.2023.10.001
PMID: 37827458 [Indexed for MEDLINE]

Conflict of interest statement: Declaration of Competing Interest CL is supported by the German Center for Infection Research (DZIF) under grant TTU

02.709. The other authors declare no conflict of interests.

59. Status of HIV and comorbidities in refugees with HIV from Ukraine.

HIV Med. 2023 Dec 3. doi: 10.1111/hiv.13597. Online ahead of print.

Ahrenstorf G(1), Dopfer-Jablonka A(1)(2), Joean O(3), Knuth C(1), Silchmueller M(1), Thiele T(1), Ringshausen FC(3)(4), Slevogt H(3)(5), Witte T(1)(6), Behrens GMN(1)(2)(5).

PURPOSE: To describe the clinical characteristics of refugees with HIV from Ukraine that seek continuation of medical care in Germany.

METHODS: Fourty-six refugees with HIV that had left Ukraine between 24 February and 30 December 2022 were examined. Information on patients' history was obtained using a standardized questionnaire for clinical care. Interviews were conducted in Russian during their first clinical presentation.

RESULTS: Fourty-six persons (41 females and 5 males) were included and their mean age was 39.6 (±8.4) years. The mean time since HIV diagnosis was 8.0 (median, IQR 7.15) years and 70.3% of participants currently received tenfofovir-DF, lamividine and dolutegravir. Most refugees had an undetectable HIV viral load and their current mean CD4 T cell count was 702 (SD ± 289) per µL. Serology revealed previous hepatitis B infection in 50.4% without evidence for replication, with undetectable anti-hepatitis B surface antigen in the remaining refugees. Antibodies against hepatitis C were present in 23 refugees (50%), but only 10 patients had been diagnosed with hepatitis C previously. Five refugees had undergone successful antiviral treatment for hepatitis C. Detectable HCV-RNA was evident in nine patients (19.6%). Sixteen (38.6%) refugees had a positive tuberculosis (TB) interferon gamma release assay, and four were on TB treatment for previously diagnosed infection. One had been diagnosed with multidrug-resistant (MDR) TB, two with pre-extensively drug-resistant (pre-XDR) TB and two with XDR TB and were treated with combinations of second-line and novel agents according to WHO guidelines.

CONCLUSIONS: Based on this preliminary analysis of a not fully representative cohort, refugees with HIV from Ukraine were young, mostly healthy females highly adherent to antiretroviral therapy. The rate of transmittable co-infections urges early diagnostic evaluation and treatment.

DOI: 10.1111/hiv.13597

PMID: 38043508

60. Outcomes from a national screening program for Ukrainian refugees at risk of drug resistant tuberculosis in Wales.

Thorax. 2023 Dec 15;79(1):86-89. doi: 10.1136/thorax-2023-220161.

Barry SM(1)(2), Davies G(3), Barry TD(4), Evans J(5), Backx M(6), Brouns M(7), Mughal A(8), Kelly S(9), Collier G(10), Ambalavanan S(11), Davies C(3), Sharp H(3), Lloyd P(9), Hester Y(12), Murray N(13), Goddard K(14), Johnstone L(8), Parry J(15), Davies O(15), Williams R(13), Ahern G(16), Smith J(16).

High rates of drug-resistant tuberculosis in Ukraine suggest screening is necessary to mitigate public health hazards for host populations. A pathway was implemented in Wales and data prospectively collected Between 8 April and 21 December 2022. Of 5425 Ukrainian arrivals, notifications were received by TB teams on 2395 (44%) of whom 1955 (82%) were screened. The refugees were young (median age 30, IQR 14-41), and predominantly female (66.1%). Interferon- gamma release assay (IGRA) tests were positive in 112 (6.5%). One Case of active tuberculosis was identified (0.05%). Our data supports European guidelines that routine screening of this population is not recommended, but we remain uncertain as to the risks of this population going forwards.

DOI: 10.1136/thorax-2023-220161
PMID: 37344177 [Indexed for MEDLINE]

Conflict of interest statement: Competing interests: None declared.

61. Structural Optimization of Antimycobacterial Azaaurones Towards Improved Solubility and Metabolic Stability.

ChemMedChem. 2023 Dec 14;18(24):e202300410. doi: 10.1002/cmdc.202300410. Epub 2023 Nov 6.

Campaniço A(1), Harjivan SG(1), Freitas E(1), Serafini M(1), Gaspar MM(1), Capela R(1), Gomes P(1), Jordaan A(2), Madureira AM(1), André V(3)(4), Silva AB(5), Duarte MT(3), Portugal I(1), Perdigão J(1), Moreira R(1), Warner DF(2)(6), Lopes F(1).

While N-acetyl azaaurones have already been disclosed for their potential against tuberculosis (TB), their low metabolic stability remains an unaddressed

liability. We now report a study designed to improve the metabolic stability and solubility of the azaaurone scaffold and to identify the structural requirements for antimycobacterial activity. Replacing the N-acetyl moiety for a N-carbamoyl group led to analogues with sub- and nanomolar potencies against M. tuberculosis H37Rv, as well as equipotent against drug-susceptible and drug-resistant M. tuberculosis isolates. The new N-carbamoyl azaaurones exhibited improved microsomal stability, compared to their N-acetylated counterparts, with several compounds displaying moderate to high kinetic solubility. The frequency of spontaneous resistance to azaaurones was observed to be in the range of 10-8 , a value that is comparable to current TB drugs in the market. Overall, these results reveal that azaaurones are amenable to structural modifications to improve metabolic and solubility liabilities, and highlight their potential as antimycobacterial agents.

DOI: 10.1002/cmdc.202300410
PMID: 37845182 [Indexed for MEDLINE]

62. Discovery of novel and potent InhA direct inhibitors by ensemble docking-based virtual screening and biological assays.

J Comput Aided Mol Des. 2023 Dec;37(12):695-706. doi: 10.1007/s10822-023-00530-4. Epub 2023 Aug 29.

Zhang Q(1)(2), Han J(3), Zhu Y(3), Yu F(2), Hu X(1), Tong HHY(1), Liu H(4).

Multidrug-resistant tuberculosis (MDR-TB) continues to spread worldwide and remains one of the leading causes of death among infectious diseases. The enoyl-acyl carrier protein reductase (InhA) belongs to FAS-II family and is essential for the formation of the Mycobacterium tuberculosis cell wall. Recent years, InhA direct inhibitors have been extensively studied to overcome MDR-TB. However, there are still no inhibitors that have entered clinical research. Here, the ensemble docking-based virtual screening along with biological assay were used to identify potent InhA direct inhibitors from Chembridge, Chemdiv, and Specs. Ultimately, 34 compounds were purchased and first assayed for the binding affinity, of which four compounds can bind InhA well with KD values ranging from 48.4 to 56.2 μM. Among them, compound 9,222,034 has the best inhibitory activity against InhA enzyme with an IC50 value of 18.05 μM. In addition, the molecular dynamic simulation and binding free energy calculation indicate that the identified compounds bind to InhA with "extended" conformation. Residue energy decomposition shows that residues such as Tyr158, Met161, and Met191 have higher energy contributions in the binding of compounds. By analyzing the binding modes, we found that these compounds can bind to a

hydrophobic sub-pocket formed by residues Tyr158, Phe149, Ile215, Leu218, etc., resulting in extensive van der Waals interactions. In summary, this study proposed an efficient strategy for discovering InhA direct inhibitors through ensemble docking-based virtual screening, and finally identified four active compounds with new skeletons, which can provide valuable information for the discovery and optimization of InhA direct inhibitors.

DOI: 10.1007/s10822-023-00530-4
PMID: 37642861 [Indexed for MEDLINE]

63. Virtual screening and identification of promising therapeutic compounds against drug-resistant Mycobacterium tuberculosis β-ketoacyl-acyl carrier protein synthase I (KasA).

J Biomol Struct Dyn. 2023 Dec 13:1-13. doi: 10.1080/07391102.2023.2293276. Online ahead of print.

Andrianov AM(1), Furs KV(2), Gonchar AV(2), Skrahina AM(3), Wang Y(4), Lyu LD(4)(5), Tuzikov AV(2).

The emergence of new Mycobacterium tuberculosis (Mtb) strains resistant to the key drugs currently used in the clinic for tuberculosis treatment can substantially reduce the probability of therapy success, causing the relevance and importance of studies on the development of novel potent antibacterial agents targeting different vulnerable spots of Mtb. In this study, 28,860 compounds from the library of bioactive molecules were screened to identify novel potential inhibitors of β-ketoacyl-acyl carrier protein synthase I (KasA), one of the key enzymes involved in the biosynthesis of mycolic acids of the Mtb cell wall. In doing so, we used a structure-based virtual screening approach to drug repurposing that included high-throughput docking of the C171Q KasA enzyme with compounds from the library of bioactive molecules including the FDA-approved drugs and investigational drug candidates, assessment of the binding affinity for the docked ligand/C171Q KasA complexes, and molecular dynamics simulations followed by binding free energy calculations. As a result, post-modeling analysis revealed 6 top-ranking compounds exhibiting a strong attachment to the malonyl binding site of the enzyme, as evidenced by the values of binding free energy which are significantly lower than those predicted for the KasA inhibitor TLM5 used in the calculations as a positive control. In light of the data obtained, the identified compounds are suggested to form a good basis for the development of new antitubercular molecules of clinical significance with activity against the KasA enzyme of Mtb.Communicated by

Ramaswamy H. Sarma.

DOI: 10.1080/07391102.2023.2293276
PMID: 38088766

64. Combined Retrospective-Prospective Cohort Study to Know the Risk of Sensorineural Hearing Loss in Patients of Drug Resistant TB Receiving Anti Tuberculous Treatment (ATT) at Tertiary Care Centre in South Gujarat.

Indian J Otolaryngol Head Neck Surg. 2023 Dec;75(4):3185-3190. doi: 10.1007/s12070-023-03702-8. Epub 2023 Jun 15.

Bhavsar KN(1), Chaudhari AV(2), Chauhan JM(1), Patel RB(1), Contractor JA(1), Shamaliya KD(3), Desai PJ(1), Roy PP(1), Patel HC(4).

Combined retrospective-prospective cohort study was done to know the risk of sensorineural hearing loss in patients of drug resistant Tuberculosis (TB) receiving Anti Tuberculous Treatment (ATT) at tertiary care centre in South Gujarat. Study was done by using retrospective and prospective data of the patients of drug resistant TB of NCHS who received injectable ATT and referred by department of Respiratory Medicine to ENT department for purpose of hearing evaluation pre and post treatment (Case cohort). Age and sex matched control cohort was also used which includes patients of non-drug resistant TB who were not receiving Injectable ATT. Incidence of SNHL in patients taking ATT for drug resistant tuberculosis in our study was 33.9%. The Relative Risk of SNHL was 14.3%. The Attributable Risk of SNHL (preventable SNHL) was 93%.

DOI: 10.1007/s12070-023-03702-8
PMCID: PMC10645687
PMID: 37974733

Conflict of interest statement: Conflict of interestThe authors have no financial or non-financial intrest to disclose.

65. Deciphering insights into the binding mechanism and plasticity of Telacebec with M. tuberculosis cytochrome bcc-aa3 supercomplex through an unbiased molecular dynamics simulation, free-energy analysis, and DFT study.

J Biomol Struct Dyn. 2023 Dec 18:1-14. doi: 10.1080/07391102.2023.2294833. Online ahead of print.

Ray B(1), Roy KK(1).

The cytochrome bcc-aa3 supercomplex, a key component in the electron transport chain pathway involved in bacterial energy production and homeostasis, is a clinically validated target for tuberculosis (TB), leading to Telacebec (Q203). Telacebec is a potent candidate drug under Phase II clinical development for the treatment of drug-sensitive and drug-resistant TB. Recently, the cryo-electron microscopy structure of this supercomplex from Mycobacterium tuberculosis (Mtb) complexed with Q203 was resolved at 6.9 Å resolution (PDB ID: 7E1W). To understand the binding site (QP site) flexibility and Q203's stability at the QP site of the Mtb cytochrome bcc complex, we conducted molecular dynamics (MD) simulation and free energy analysis on this complex in an explicit hydrated lipid bilayer environment for 500 ns. Through this study, the persistence of a range of direct and indirect interactions was observed over the course of the simulation. The significance of the interactions with His375, Tyr161, Ala178, Ala179, Ile183, His355, Leu356, and Thr313 is underlined. Electrostatic energy was the primary source of the net binding free energy, regardless of the important interacting residues. The overall binding free energy for Q203 was -112.84 ± 7.73 kcal/mol, of which the electrostatic and lipophilic energy contributions were -116.31 ± 1.14 and -21.32 ± 2.35 kcal/mol, respectively. Meanwhile, DFT calculations were utilized to elucidate Q203's molecular properties. Overall, this study deciphers key insights into the cytochrome bcc-aa3 supercomplex with Q203 on the ground of molecular mechanics and quantum mechanics that may facilitate structure-based drug design and optimization for the discovery of the next-generation antitubercular drug(s).Communicated by Ramaswamy H. Sarma.

DOI: 10.1080/07391102.2023.2294833
PMID: 38111165

66. Targeted next-generation sequencing technology showed great potential in identifying spinal tuberculosis and predicting the drug resistance.

J Infect. 2023 Dec;87(6):e110-e112. doi: 10.1016/j.jinf.2023.10.018. Epub 2023 Oct 26.

Zhang G(1), Zhang H(2), Zhang Y(3), Hu X(4), Tang M(5), Gao Q(6).

DOI: 10.1016/j.jinf.2023.10.018

PMID: 37898411 [Indexed for MEDLINE]

Conflict of interest statement: Declaration of Competing Interest The authors declare that the research was conducted in the absence of any commercial relations or financial relationships of interest that might be a constant of interest.

67. Toxicological Profiling of Potential Shikimate Kinase Inhibitors Against Mycobacterium tuberculosis.

Altern Lab Anim. 2023 Dec 14:2611929231217062. doi: 10.1177/02611929231217062. Online ahead of print.

Jhangiani A(1), Panda V(1), Sukheja A(1), Thomas S(1), Dusseja P(1), Pandya S(2), Chintakrindi A(3).

Over the last decade, Mycobacterium tuberculosis has mutated into a putative 'superbug', as treatments against it have failed due to increasing antimicrobial resistance. As a result, the rising incidence of multidrug-resistant tuberculosis (MDR-TB) is posing a significant public health threat, thus, the need to develop effective drugs for MDR-TB has become an urgent priority. To identify new drug candidates for the treatment of MDR-TB, the present study was based on mycobacterial shikimate kinase (MtSK) as the pharmacological target. One hundred potential MtSK inhibitors were identified from literature and database searches to identify compounds that were designed to specifically function as MtSK antagonists. The ADME properties of these compounds were evaluated by using the SwissADME web tool. ProTox-II software was also used to investigate any potential endocrine disrupting effects, mediated through their interaction with oestrogenic and/or androgenic receptors. This study also aimed to predict LD50 values of potential drug candidates that would be active against the standard H37Rv strain of M. tuberculosis, by using the ProTox-II in silico tool. The molecules for which no structural hazard alerts were identified with these software tools were further subjected to molecular docking analyses and molecular dynamic simulations to estimate their ability to interact with the MtSK enzyme. Preliminary results from SwissADME indicated that 30 molecules were drug-like, due to their physicochemical and pharmacokinetic properties. However, subsequent analysis with ToxTree and ProTox-II indicated that only three of these 30 drug-like molecules were suitable for taking forward into further in vitro experiments. This study, which is based on the use of commonly used open-source in silico tools, identified new MtSK ligands for potential use in the development of new drugs for the therapeutic management of tuberculosis. An initial prediction of their safety profile was also generated.

DOI: 10.1177/02611929231217062

PMID: 38095084

Conflict of interest statement: Declaration of conflicting interestsThe author(s) declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

68. Direct Detection of Fluoroquinolone Resistance in Sputum Samples from Tuberculosis Patients by High Resolution Melt Curve Analysis.

Curr Microbiol. 2023 Dec 2;81(1):27. doi: 10.1007/s00284-023-03519-2.

Gupta RK(#)(1)(2), Anthwal D(#)(1)(2), Bhalla M(3), Tyagi JS(4), Choudhary S(2), Haldar S(5)(6).

Multidrug-resistant tuberculosis (MDR-TB) requires treatment with fluoroquinolone (FLQ) drugs, however, the excessive use of FLQ has led to the rise of extensively drug-resistant TB. In 2019, ~ 20% of total MDR-TB cases were estimated to be resistant to FLQ drugs. In the present study, we developed and evaluated the utility of high-resolution melt curve analysis (HRM) for the rapid detection of FLQ-resistant Mycobacterium tuberculosis for the first time directly from sputum samples. A reference plasmid library was generated for the most frequently observed mutations of gyrA gene and was used to discriminate between mutant and wild-type samples in the FLQ-HRM assay. The developed assay was evaluated on n = 25 MDR M. tuberculosis clinical isolates followed by validation on archived sputum DNA (n = 88) using DNA sequencing as a gold standard. The FLQ-HRM assay showed a 100% sensitivity [95% Confidence Interval (CI): 71.5 to 100] and specificity (95% CI: 39.7 to 100) in smear-positive category, and a sensitivity of 88.9% (95% CI: 77.3 to 95.8) with 84.2% (95% CI: 60.4 to 96.6) specificity in smear-negative category. The assay showed a high level of concordance of ~ 90% (κ = 0.74) with DNA sequencing, however, we were limited by the absence of phenotypic drug susceptibility testing data. In conclusion, HRM is a rapid, cost-effective (INR 150/USD 1.83) and closed-tube method for direct detection of FLQ resistance in sputum samples including direct smear-negative samples.

DOI: 10.1007/s00284-023-03519-2
PMID: 38041739 [Indexed for MEDLINE]

69. A bedaquiline, pyrazinamide, levofloxacin, linezolid, clofazimine second line regimen for tuberculosis displays similar early bactericidal activity as the

standard rifampin based first line regimen.

J Infect Dis. 2023 Dec 7:jiad564. doi: 10.1093/infdis/jiad564. Online ahead of print.

Zainabadi K(1), Vilbrun SC(2), Mathurin LD(2), Walsh KF(1)(3), Pape JW(1)(2), Fitzgerald DW(1), Lee MH(1).

BACKGROUND: In 2018 the World Health Organization (WHO) recommended a switch to an all oral bedaquiline based second line regimen for treatment of drug resistant (DR) tuberculosis (TB). How these new second line regimens fare in comparison to first line regimens for treatment of drug sensitive (DS) tuberculosis is not well known.
METHODS: In this study, we contemporaneously enrolled subjects with DS (n = 31) and DR (n = 23) TB and assessed their response to therapy with first-line (rifampin, isoniazid, ethambutol, pyrazinamide) or second-line (bedaquiline, pyrazinamide, levofloxacin, linezolid, clofazimine) regimens, respectively.
RESULTS: We found that the early bactericidal activity of first and second line regimens was similar during the first two weeks of therapy as determined by BACTEC MGIT, colony forming units (CFU), and a liquid limiting dilution (LD) assays capable of detecting differentially detectable/culturable Mtb (DD Mtb). Further, an identical percentage (77.8%) of subjects from the DS and DR cohorts converted to culture negative after two months of therapy.
CONCLUSIONS: Despite presenting with more advanced disease at time of treatment, subjects with DR TB receiving an all oral bedaquiline based second line treatment regimen displayed a similar microbiological response to therapy as subjects with DS TB receiving a first-line treatment regimen.

DOI: 10.1093/infdis/jiad564
PMID: 38060827

70. Monitoring of First-line Drug Resistance Mutations Outside the Scope of Xpert MTB/RIF Ultra is Needed for Successful Control of DR-TB in Southern Mozambique.

Clin Infect Dis. 2023 Dec 4:ciad684. doi: 10.1093/cid/ciad684. Online ahead of print.

Mariner-Llicer C(1), Saavedra Cervera B(2)(3), Mambuque E(3), Gomes N(3), Munguambe S(3), Villamayor L(4), Cancino-Muñoz I(4)(5), Torres-Puente M(1), Nguenha D(3)(6), Respeito D(3), Tembe G(3), López MG(1), Comas I(1)(7), García-Basteiro AL(2)(3)(8).

Multidrug-resistant(MDR) tuberculosis in Southern Africa is of great concern, exacerbated by the spread of a clone harboring a mutation missed by Xpert Ultra. In Southern Mozambique, the presence of such mutation and rising cases of non-MDR isoniazid resistance highlights the need to ensure accurate detection of antimicrobial-resistance in the country.

DOI: 10.1093/cid/ciad684
PMID: 38048599

Conflict of interest statement: Potential conflicts of interest. I. C. received consultancy fees from Foundation for innovative new diagnostics for the development of the WHO mutation catalogue v1. 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.

71. Whole genome sequencing reveals candidate genes involving in PAS resistance in M. Tuberculosis isolated from patients in Thailand.

World J Microbiol Biotechnol. 2023 Dec 7;40(1):32. doi: 10.1007/s11274-023-03834-7.

Dokladda K(1), Billamas P(2), Jaitrong S(2), Suwanakitti N(2), Phornsiricharoenphant W(2), Viratyosin W(2), Prammananan T(2).

Para-amino salicylic acid (PAS) was first reported by Lehmann in 1946 and used for tuberculosis treatment. However, due to its adverse effects, it is now used only as a second line anti-tuberculosis drug for treatment of multidrug resistant or extensively drug resistant M. tuberculosis. The structure of PAS is similar to para-amino benzoic acid (pABA), an intermediate metabolite in the folate synthesis pathway. The study has identified mutations in genes in folate pathway and their intergenic regions for their possibilities in responsible for PAS resistance. Genomic DNA from 120 PAS-resistant and 49 PAS-sensitive M. tuberculosis isolated from tuberculosis patients in Thailand were studied by whole genome sequencing. Twelve genes in the folate synthesis pathway were investigated for variants associated with PAS resistance. Fifty-one SNVs were found in nine genes and their intergenic regions (pabC, pabB, folC, ribD, thyX, dfrA, thyA, folK, folP). Functional correlation test confirmed mutations in RibD, ThyX, and ThyA are responsible for PAS resistance. Detection of mutation in thyA, folC, intergenic regions of thyX, ribD, and double deletion of thyA

dfrA are proposed for determination of PAS resistant M. tuberculosis.

DOI: 10.1007/s11274-023-03834-7
PMID: 38057660 [Indexed for MEDLINE]

72. Assessing patient satisfaction with video-supported therapy for drug-susceptible TB treatment.

Int J Tuberc Lung Dis. 2023 Dec 1;27(12):938-940. doi: 10.5588/ijtld.23.0227.

Ragheb SM(1), White JB(2), Jarand J(3), Fisher DA(3), Lim RK(3).

DOI: 10.5588/ijtld.23.0227
PMID: 38042971 [Indexed for MEDLINE]

73. Screening with GenoType(®) MTBDRplus shortens the time to MDR-TB treatment initiation but does not change outcomes.

Int J Tuberc Lung Dis. 2023 Dec 1;27(12):949-951. doi: 10.5588/ijtld.23.0096.

Mendoza-Ticona A(1), Mitnick CD(2), Obregón G(3), Alarcón V(4).

DOI: 10.5588/ijtld.23.0096
PMID: 38042965 [Indexed for MEDLINE]