October Literature

1. **Genetic Diversity and Drug Susceptibility Profiles of Multidrug-Resistant Tuberculosis Strains in Southeast China.**

Infect Drug Resist. 2021 Sep 28;14:3979-3989. doi: 10.2147/IDR.S331516. eCollection 2021.

Lin S(1), Wei S(1), Zhao Y(1), Dai Z(1), Lin J(1), Pang Y(2).

BACKGROUND: Multidrug-resistant tuberculosis (MDR-TB) isolates collected from Fujian province, China were assessed for molecular epidemiological characteristics. Analysis of isolate genotype profiles revealed that the Beijing genotype was associated with especially high drug resistance and community transmission rates.
METHODS: A total of 119 MDR-TB isolates obtained from TB patients in Fujian province were typed using 24-locus mycobacterium interspersed repetitive unit-variable number tandem repeat (MIRU-VNTR) typing and spoligotyping. Drug susceptibility testing of all isolates was conducted using the L-J proportion method, with pyrazinamide (PZA) susceptibility testing conducted using the Mycobacterium Growth Indicator Tube System 960 (MGIT 960).
RESULTS: We obtained 26 spoligotypes for the 119 isolates examined in this work. Spoligotyping results revealed that 80 (67.2%) isolates possessed the Beijing family genotypic profiles. Patients aged 25-44 years and ≥45 years were most likely to be infected by non-Beijing genotypes. The percentage of clustered cases with both PZA and ofloxacin (OFLX) resistance was significantly greater than the corresponding percentage for non-clustered cases. Of 44 PZA-resistant isolates, 28 isolates (63.6%) harbored pncA mutations, while pncA mutations were only detected in 7 (9.3%) PZA-susceptible isolates.
CONCLUSION: Our data demonstrate that the Beijing genotype is the dominant lineage among MDR-TB strains circulating in Fujian. Thus, MDR-TB infections occurring within this province are not likely associated with recent transmission events. PZA and fluoroquinolone resistance profiles were found to be associated with clustered isolates. Mutation of pncA is the main driver of MDR-TB PZA resistance and is associated with mutation sites scattered throughout the entire pncA protein-coding region.

DOI: 10.2147/IDR.S331516
PMCID: PMC8487280
PMID: 34611415

2. **Electronic Dose Monitoring Identifies a High-Risk Subpopulation in the Treatment of Drug-resistant Tuberculosis and Human Immunodeficiency Virus.**

Clin Infect Dis. 2021 Oct 5;73(7):e1901-e1910. doi: 10.1093/cid/ciaa1557.

Zelnick JR(1), Daftary A(2)(3), Hwang C(4), Labar AS(5), Boodhram R(3), Maharaj B(3), Wolf AK(6), Mondal S(7), Amico KR(8), Orrell C(9), Seepamore B(10), Friedland G(11), Padayatchi N(3), O'Donnell MR(3)(4)(6).

BACKGROUND: In generalized drug-resistant tuberculosis (DR-TB) human immunodeficiency virus (HIV) epidemics, identifying subpopulations at high risk for treatment failure and loss to care is critically important to improve treatment outcomes and prevent amplification of drug resistance. We hypothesized that an electronic dose-monitoring (EDM) device could empirically identify adherence-challenged patients and that a mixed-methods approach would characterize treatment challenges.
METHODS: A prospective study of patients with DR-TB HIV on antiretroviral therapy (ART) initiating bedaquiline-containing regimens in KwaZulu-Natal, South Africa. Separate EDM devices measured adherence for bedaquiline and ART. Patients with low adherence (<85%) to both bedaquiline and ART were identified as high risk for poor outcomes. Baseline survey, study visit notes, and focus group discussions characterized treatment challenges.
RESULTS: From December 2016-February 2018, 32 of 198 (16%) enrolled patients with DR-TB HIV were identified as dual-adherence challenged. In a multivariate model including baseline characteristics, only receiving a disability grant was significantly associated with dual nonadherence at 6 months. Mixed-methods identified treatment barriers including alcohol abuse, family conflicts, and mental health issues. Compared with adherent patients, dual-adherence-challenged patients struggled to prioritize treatment and lacked support, and dual-adherence-challenged patients experienced higher rates of detectable HIV viral load and mortality than more adherent patients.
CONCLUSIONS: EDM empirically identified a subpopulation of patients with DR-TB HIV with dual-adherence challenges early in treatment. Mixed-methods revealed intense psychosocial, behavioral, and structural barriers to care in this subpopulation. Our data support developing differential, patient-centered, adherence support interventions focused on psychosocial and structural challenges for subpopulations of at-risk DR-TB HIV patients.

DOI: 10.1093/cid/ciaa1557

PMCID: PMC8492155
PMID: 33053186

3. **Individualised treatment for multidrug-resistant tuberculosis in New South Wales, Australia.**

Aust N Z J Public Health. 2021 Oct;45(5):437-442. doi: 10.1111/1753-6405.13144. Epub 2021 Jul 26.

Chang V(1)(2), Ling R(1), Velen K(1), Fox G(1)(3).

OBJECTIVE: Multidrug-resistant tuberculosis (MDR-TB) presents a major global health challenge. In high-income countries, treatment is individualised to optimise efficacy and reduce toxicity. We aimed to evaluate the outcomes of patients with MDR-TB receiving individualised antibiotic therapy in Australia.
METHODS: This retrospective cohort study was performed in the city of Sydney in Australia and included patients diagnosed with bacteriologically confirmed MDR-TB diagnosed between 2000 and 2016. The clinical characteristics of patients and treatment details were extracted from medical records. The incidence of adverse events and end-of-treatment outcomes were also evaluated.
RESULTS: Fifty-five patients with MDR-TB were identified at TB clinics in seven hospitals. The median age was 32 years (interquartile range [IQR]: 27-36 years). The median duration of the intensive phase treatment was six months (IQR 6-7 months). All patients' treatment administration was directly observed. The commonest reported adverse event was ototoxicity (44%; 23/52) and successful treatment outcomes were achieved by 95% (52/55) of patients.
CONCLUSION: This study demonstrated the high treatment success rate that can be achieved using individualised treatment for MDR-TB in a well-resourced setting. Implications for public health: The expansion of individualised therapy promises to contribute to MDR-TB control and advance the ambitious goal of TB elimination by 2035.

DOI: 10.1111/1753-6405.13144
PMID: 34309967

4. **Design of Multidrug-Resistant Tuberculosis Treatment Regimens Based on DNA Sequencing.**

Clin Infect Dis. 2021 Oct 5;73(7):1194-1202. doi: 10.1093/cid/ciab359.

Grobbel HP(1)(2)(3), Merker M(2)(4), Köhler N(1)(2)(3), Andres S(5), Hoffmann H(6)(7), Heyckendorf J(1)(2)(3), Reimann M(1)(2)(3), Barilar I(4), Dreyer V(4), Hillemann D(5), Kalsdorf B(1)(2)(3), Kohl TA(4), Sanchez Carballo P(1)(2)(3), Schaub D(1)(2)(3), Todt K(6)(7), Utpatel C(4), Maurer FP(5)(8), Lange C(1)(2)(3)(9), Niemann S(2)(4)(5).

BACKGROUND: Comprehensive and reliable drug susceptibility testing (DST) is urgently needed to provide adequate treatment regimens for patients with multidrug-resistant/rifampicin-resistant tuberculosis (MDR/RR-TB). We determined whether next-generation sequencing (NGS) analysis of Mycobacterium tuberculosis complex isolates and genes implicated in drug resistance can guide the design of effective MDR/RR-TB treatment regimens.
METHODS: NGS-based genomic DST predictions of M. tuberculosis complex isolates from MDR/RR-TB patients admitted to a TB reference center in Germany between 1 January 2015 and 30 April 2019 were compared with phenotypic DST results of mycobacteria growth indicator tubes (MGIT). Standardized treatment algorithms were applied to design individualized therapies based on either genomic or phenotypic DST results, and discrepancies were further evaluated by determination of minimal inhibitory drug concentrations (MICs) using Sensititre MYCOTBI and UKMYC microtiter plates.
RESULTS: In 70 patients with MDR/RR-TB, agreement among 1048 pairwise comparisons of genomic and phenotypic DST was 86.3%; 76 (7.2%) results were discordant, and 68 (6.5%) could not be evaluated due to the presence of polymorphisms with yet unknown implications for drug resistance. Importantly, 549 of 561 (97.9%) predictions of drug susceptibility were phenotypically confirmed in MGIT, and 27 of 64 (42.2%) false-positive results were linked to previously described mutations mediating a low or moderate MIC increase. Virtually all drugs (99.0%) used in combination therapies that were inferred from genomic DST were confirmed to be susceptible by phenotypic DST.
CONCLUSIONS: NGS-based genomic DST can reliably guide the design of effective MDR/RR-TB treatment regimens.

DOI: 10.1093/cid/ciab359
PMCID: PMC8492214
PMID: 33900387

5. **Causes of multidrug-resistant tuberculosis from the perspectives of health providers: challenges and strategies for adherence to treatment during the COVID-19 pandemic in Brazil.**

BMC Health Serv Res. 2021 Oct 1;21(1):1033. doi: 10.1186/s12913-021-07057-0.

Souza LLL(1), Santos FLD(2), Crispim JA(3), Fiorati RC(4), Dias S(5), Bruce ATI(2), Alves YM(6), Ramos ACV(6), Berra TZ(6), da Costa FBP(6), Alves LS(6), Monroe AA(7), Fronteira I(8), Arcêncio RA(7).

BACKGROUND: Multidrug-resistant tuberculosis (MDR-TB) is a serious phenomenon on a global scale that can worsen with the COVID-19 pandemic. The study aimed to understand the perceptions of health professionals about MDR-TB, their strategies to ensure adherence to treatment and their challenges in the context of the COVID-19 pandemic in a priority municipality for disease control.
METHODS: We conducted a qualitative study and recruited 14 health providers (four doctors, three nurses, three nursing technicians, three nursing assistants and a social worker) working in a city in the state of São Paulo, Brazil. Remote semi-structured interviews were conducted with the participants. For data analysis, the thematic content analysis technique was applied according to the study's theoretical framework.
RESULTS: The study revealed the causes of MDR-TB are associated with poverty, vulnerability, and social risk. A pre-judgement from the providers was observed, namely, all patients do not adhere due their resistance and association with drug abuse or alcoholism. The study also observed difficulty among health providers in helping patients reconstruct and reframe their life projects under a care perspective, which would strengthen adherence. Other issues that weakened adherence were the cuts in social protection and the benefits really necessary to the patients and a challenge for the providers manage that. The participants revealed that their actions were impacted by the pandemic and insecurity and fear manifested by patients after acquiring COVID-19. For alleviating this, medical appointments by telephone, delivery of medicine in the homes of patients and visits by health professionals once per week were provided.
CONCLUSION: The study advances knowledge by highlighting the challenges faced by the health system with the adherence of patients with MDR-TB in a context aggravated by the pandemic. An improvement in DOT is really necessary to help the patients reframe their lives without prejudices, face their fears and insecurity, recover their self-esteem and motivate in concluding their treatment.

DOI: 10.1186/s12913-021-07057-0
PMCID: PMC8483800
PMID: 34592970 [Indexed for MEDLINE]

6. **Drug resistance and its risk factors among extrapulmonary tuberculosis in**

Ethiopia: A systematic review and meta-analysis.

PLoS One. 2021 Oct 8;16(10):e0258295. doi: 10.1371/journal.pone.0258295. eCollection 2021.

Diriba G(1), Tola HH(1), Alemu A(1), Yenew B(1), Gamtesa DF(1), Kebede A(1)(2).

BACKGROUND: Drug-resistant tuberculosis and extrapulmonary tuberculosis are the world major public health issues. Although some primary studies have been reported on the burden of drug-resistant tuberculosis in extrapulmonary tuberculosis patients in Ethiopia, there is no systematic review and meta-analysis that attempt to summarize the available literature. Thus, we aimed to estimates the prevalence of drug-resistance in extrapulmonary tuberculosis patients and summarize the risk factors associated with the occurrence of extrapulmonary tuberculosis in Ethiopia.
METHODS: We conducted a systematic review of the published primary studies on extrapulmonary drug-resistant tuberculosis in Ethiopia.
RESULTS: Eight observational studies were included in this review from different regions of Ethiopia. The overall pooled prevalence of rifampicin resistance was 6% (95% CI 0.03-0.10), while isoniazid resistance was 7% (95% CI 0.03-0.12). The pooled prevalence of multidrug-resistant tuberculosis was 4% (95% CI 0.01-0.07). Previous tuberculosis treatment history and male gender are frequently reported risk factors for developing drug-resistant tuberculosis in extrapulmonary tuberculosis patients.
CONCLUSION: The current review has identified a high proportion of resistance to rifampicin, isoniazid, and multidrug-resistant tuberculosis in patients with extrapulmonary tuberculosis in Ethiopia. Clinicians should request drug susceptibility testing for all patients with presumptive extrapulmonary tuberculosis to detect drug-resistance.

DOI: 10.1371/journal.pone.0258295
PMCID: PMC8500428
PMID: 34624050

7. **Rifampicin-Monoresistant Tuberculosis Is Not the Same as Multidrug-Resistant Tuberculosis: a Descriptive Study from Khayelitsha, South Africa.**

Antimicrob Agents Chemother. 2021 Oct 18;65(11):e0036421. doi: 10.1128/AAC.00364-21. Epub 2021 Aug 30.

Salaam-Dreyer Z(1), Streicher EM(2), Sirgel FA(2), Menardo F(3)(4), Borrell S(3)(4), Reinhard M(3)(4), Doetsch A(3)(4), Cudahy PGT(5), Mohr-Holland E(6), Daniels J(6), Dippenaar A(7), Nicol MP(8), Gagneux S(3)(4), Warren RM(2), Cox

H(1)(9).

Rifampin monoresistance (RMR; rifampin resistance and isoniazid susceptibility) accounts for 38% of all rifampin-resistant tuberculosis (RR-TB) in South Africa and is increasing. We aimed to compare RMR-TB with multidrug-resistant TB (MDR-TB) in a setting with high TB, RR-TB, and HIV burdens. Patient-level clinical data and stored RR Mycobacterium tuberculosis isolates from 2008 to 2017 with available whole-genome sequencing (WGS) data were used to describe risk factors associated with RMR-TB and to compare RR-conferring mutations between RMR-TB and MDR-TB. A subset of isolates with particular RR-conferring mutations were subjected to semiquantitative rifampin phenotypic drug susceptibility testing. Among 2,041 routinely diagnosed RR-TB patients, 463 (22.7%) had RMR-TB. HIV-positive individuals (adjusted odds ratio [aOR], 1.4; 95% confidence interval [CI], 1.1 to 1.9) and diagnosis between 2013 and 2017 versus between 2008 and 2012 (aOR, 1.3; 95% CI, 1.1 to 1.7) were associated with RMR-TB. Among 1,119 (54.8%) patients with available WGS data showing RR-TB, significant differences in the distribution of rpoB RR-conferring mutations between RMR and MDR isolates were observed. Mutations associated with high-level RR were more commonly found among MDR isolates (811/889 [90.2%] versus 162/230 [70.4%] among RMR isolates; $P < 0.0001$). In particular, the rpoB L430P mutation, conferring low-level RR, was identified in 32/230 (13.9%) RMR isolates versus 10/889 (1.1%) in MDR isolates ($P < 0.0001$). Among 10 isolates with an rpoB L430P mutation, 7 were phenotypically susceptible using the critical concentration of 0.5 μg/ml (range, 0.125 to 1 μg/ml). The majority (215/230 [93.5%]) of RMR isolates showed susceptibility to all other TB drugs, highlighting the potential benefits of WGS for simplified treatment. These data suggest that the evolution of RMR-TB differs from MDR-TB with a potential contribution from HIV infection.

DOI: 10.1128/AAC.00364-21
PMID: 34460307

8. **Genomic-based surveillance reveals high ongoing transmission of multi-drug-resistant Mycobacterium tuberculosis in Southern Brazil.**

Int J Antimicrob Agents. 2021 Oct;58(4):106401. doi: 10.1016/j.ijantimicag.2021.106401. Epub 2021 Jul 18.

Salvato RS(1), Reis AJ(2), Schiefelbein SH(3), Gómez MAA(2), Salvato SS(4), da Silva LV(4), Costa ERD(5), Unis G(6), Dias CF(6), Viveiros M(7), Portugal I(8), von Groll A(2), da Silva PEA(2), Kritski AL(5), Perdigão J(8), Rossetti MLR(9).

Genomic-based surveillance on the occurrence of drug resistance and its transmission dynamics has emerged as a powerful tool for the control of

tuberculosis (TB). A whole-genome sequencing approach, phenotypic testing and clinical-epidemiological investigation were used to undertake a retrospective population-based study on drug-resistant (DR)-TB in Rio Grande do Sul, the largest state in Southern Brazil. The analysis included 305 resistant Mycobacterium tuberculosis strains sampled statewide from 2011 to 2014, and covered 75.7% of all DR-TB cases identified in this period. Lineage 4 was found to be predominant (99.3%), with high sublineage-level diversity composed mainly of 4.3.4.2 [Latin American and Mediterranean (LAM)/RD174], 4.3.3 (LAM/RD115) and 4.1.2.1 (Haarlem/RD182) sublineages. Genomic diversity was also reflected in resistance of the variants to first-line drugs. A large number of distinct resistance-conferring mutations, including variants that have not been reported previously in any other setting worldwide, and 22 isoniazid-monoresistant strains with mutations described as disputed in the rpoB gene but causing rifampicin resistance generally missed by automated phenotypic tests as BACTEC MGIT. Using a cut-off of five single nucleotide polymorphisms, the estimated recent transmission rate was 55.1%, with 168 strains grouped into 28 genomic clusters. The most worrying fact concerns multi-drug-resistant (MDR) strains, of which 73.4% were clustered. Different resistance profiles and acquisition of novel mutations intraclusters revealed important amplification of resistance in the region. This study described the diversity of M. tuberculosis strains, the basis of drug resistance, and ongoing transmission dynamics across the largest state in Southern Brazil, stressing the urgent need for MDR-TB transmission control state-wide.

DOI: 10.1016/j.ijantimicag.2021.106401
PMID: 34289403

9. **Evaluating newly approved drugs for multidrug-resistant tuberculosis (endTB): study protocol for an adaptive, multi-country randomized controlled trial.**

Trials. 2021 Sep 25;22(1):651. doi: 10.1186/s13063-021-05491-3.

Guglielmetti L(1)(2)(3), Ardizzoni E(4), Atger M(1), Baudin E(5), Berikova E(6)(7), Bonnet M(1)(8), Chang E(9), Cloez S(1), Coit JM(10), Cox V(11), de Jong BC(4), Delifer C(1), Do JM(10), Tozzi DDS(5), Ducher V(1), Ferlazzo G(12), Gouillou M(5), Khan A(13), Khan U(13), Lachenal N(1), LaHood AN(10), Lecca L(10)(14), Mazmanian M(1)(15), McIlleron H(16)(17), Moschioni M(1), O'Brien K(18), Okunbor O(19), Oyewusi L(20), Panda S(21)(22), Patil SB(22), Phillips PPJ(23), Pichon L(1), Rupasinghe P(4), Rich ML(10)(24)(25), Saluhuddin N(26), Seung KJ(10)(24)(25), Tamirat M(20), Trippa L(27)(28), Cellamare M(27), Velásquez GE(10)(25)(29), Wasserman S(30)(31), Zimetbaum PJ(32)(33), Varaine

F(#)(1), Mitnick CD(#)(34)(35)(36).

BACKGROUND: Treatment of multidrug- and rifampin-resistant tuberculosis (MDR/RR-TB) is expensive, labour-intensive, and associated with substantial adverse events and poor outcomes. While most MDR/RR-TB patients do not receive treatment, many who do are treated for 18 months or more. A shorter all-oral regimen is currently recommended for only a sub-set of MDR/RR-TB. Its use is only conditionally recommended because of very low-quality evidence underpinning the recommendation. Novel combinations of newer and repurposed drugs bring hope in the fight against MDR/RR-TB, but their use has not been optimized in all-oral, shorter regimens. This has greatly limited their impact on the burden of disease. There is, therefore, dire need for high-quality evidence on the performance of new, shortened, injectable-sparing regimens for MDR-TB which can be adapted to individual patients and different settings.
METHODS: endTB is a phase III, pragmatic, multi-country, adaptive, randomized, controlled, parallel, open-label clinical trial evaluating the efficacy and safety of shorter treatment regimens containing new drugs for patients with fluoroquinolone-susceptible, rifampin-resistant tuberculosis. Study participants are randomized to either the control arm, based on the current standard of care for MDR/RR-TB, or to one of five 39-week multi-drug regimens containing newly approved and repurposed drugs. Study participation in all arms lasts at least 73 and up to 104 weeks post-randomization. Randomization is response-adapted using interim Bayesian analysis of efficacy endpoints. The primary objective is to assess whether the efficacy of experimental regimens at 73 weeks is non-inferior to that of the control. A sample size of 750 patients across 6 arms affords at least 80% power to detect the non-inferiority of at least 1 (and up to 3) experimental regimens, with a one-sided alpha of 0.025 and a non-inferiority margin of 12%, against the control in both modified intention-to-treat and per protocol populations.
DISCUSSION: The lack of a safe and effective regimen that can be used in all patients is a major obstacle to delivering appropriate treatment to all patients with active MDR/RR-TB. Identifying multiple shorter, safe, and effective regimens has the potential to greatly reduce the burden of this deadly disease worldwide.
TRIAL REGISTRATION: ClinicalTrials.gov Identifier NCT02754765. Registered on 28 April 2016; the record was last updated for study protocol version 3.3, on 27 August 2019.

DOI: 10.1186/s13063-021-05491-3
PMCID: PMC8465691
PMID: 34563240 [Indexed for MEDLINE]

10. **Challenges in recruiting children to a multidrug-resistant TB prevention trial.**

Int J Tuberc Lung Dis. 2021 Oct 1;25(10):814-822. doi: 10.5588/ijtld.21.0098.

Purchase S(1), Batist E(1), Mmile N(2), Nkosi S(3), Workman J(1), Martinson N(2), Fairlie L(3), Schaaf HS(4), Choo L(5), McGowan C(5), Crook AM(5), Seddon JA(6), Hesseling AC(1).

BACKGROUND: Recruitment to randomised clinical trials can be challenging and slow recruitment has serious consequences. This study aimed to summarise and reflect on the challenges in enrolling young children to a multidrug-resistant TB (MDR-TB) prevention trial in South Africa.METHODS: Recruitment to the Tuberculosis Child Multidrug-resistant Preventive Therapy Trial (TB-CHAMP) was tracked using an electronic recruiting platform, which was used to generate a recruiting flow diagram. Structured personnel questionnaires, meeting minutes and workshop notes were thematically analysed to elucidate barriers and solutions.RESULT: Of 3,682 (85.3%) adult rifampicin (RIF) resistant index cases with pre-screening outcomes, 1597 (43.4%) reported having no children under 5 years in the household and 562 (15.3%) were RIF-monoresistant. More than nine index cases were pre-screened for each child enrolled. Numerous barriers to recruitment were identified. Thorough recruitment planning, customised tracking data systems, a dedicated recruiting team with strong leadership, adequate resources to recruit across large geographic areas, and excellent relationships with routine TB services emerged as key factors to ensure successful recruitment.CONCLUSION: Recruitment of children into MDR-TB prevention trials can be difficult. Several MDR-TB prevention trials are underway, and lessons learnt from TB-CHAMP will be relevant to these and other TB prevention studies.

DOI: 10.5588/ijtld.21.0098
PMID: 34615578

11. **Antimycobacterial activity of acetone extract and isolated metabolites from folklore medicinal lichen Usnea laevis Nyl. against drug-sensitive and multidrug-resistant tuberculosis strains.**

J Ethnopharmacol. 2022 Jan 10;282:114641. doi: 10.1016/j.jep.2021.114641. Epub 2021 Sep 15.

Tatipamula VB(1), Annam SSP(2).

ETHNOPHARMACOLOGICAL RELEVANCE: Tuberculosis (Tb) is one of the most infectious diseases caused by Mycobacterium tuberculosis (M.t) with almost 2 million deaths

yearly. Although many Tb control programs have been organised, there is an elevated number of Tb cases due to the appearance of extremely drug-resistant and multidrug-resistant (MDR) Tb strains. In the cultures of Venezuelan Andes, fruticose lichen Usnea laevis Nyl. (Usneaceae) with folklore name 'Barba de Piedra, Tusinya' is used as a natural remedy for Tb.
AIM OF THE STUDY: This study was performed to provide a scientific rationale for the folklore usage of U. laevis in treating Tb by validating its antimycobacterial activity against two drug-sensitive and four MDR-Tb strains.
MATERIALS AND METHODS: The mycobacterial inhibitory activities of acetone extract (Ul), fractions (F1-10), and isolated metabolites (1-4) of U. laevis were evaluated against M.t H37Ra using 2,3-bis-(2-methoxy-4-nitro-5-sulfophenyl)-2H-tetrazolium-5-carboxanilide reduction menadione assay (XRMA). Furthermore, Ul and 1-4 were subjected to antimycobacterial activity against M.t H37Ra, Mycobacterium smegmatis, and four MDR-Tb (MDR-A8, MDR-V791, MDR-R and MDR-40) strains using resazurin microtitre plate assay (REMA) and cytotoxicity against THP-1 macrophages using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay and their selectivity index values were also calculated.
RESULTS: Initially, Ul has shown prominent inhibitory activity (IC50 value: 5.44 ± 0.36 μg/ml) and four of its fractions (F1, F2, F5 and F7) also exhibited the best inhibitory activity (IC50 values ranged from 7.46 ± 0.19 to 71.38 ± 2.57 μg/ml) against M.t H37Ra using XRMA. Purification of these bioactive fractions identified four metabolites, namely usnic acid (1), atranorin (2), salazinic acid (3), and lobaric acid (4). From the MIC values of REMA, it was identified that Ul, 1 and 4 were more effective in inhibiting the growth of all four MDR-Tb strains, compared to first-line drug rifampicin. Interestingly, Ul has shown better antimycobacterial activity than 1-4 and rifampicin against MDR-Tb strains may be due to the synergistic effect of its metabolites. Also, the IC50 values of Ul and 1-4 on THP-1 macrophages were found to be far higher than MIC values against tested Tb strains, indicating that THP-1 macrophages were not harmfully affected at concentrations that were effective against Tb strains. Further, the calculated selectivity index values revealed the more active and non-toxicity of Ul, 1 and 4 against MDR-Tb strains than rifampicin.
CONCLUSIONS: The current study lends the first evidence for the presence of antimycobacterial metabolites in U. laevis. The results exposed the Andean folklore use of U. laevis for treating Tb, and the key biomarker metabolites were found to be 1 and 4. Hence, it can be concluded that U. laevis can be used as a potential source for the novel drug development for MDR-Tb.

DOI: 10.1016/j.jep.2021.114641
PMID: 34536516

12. **Receiving healthcare for drug-resistant TB: a cross-sectional survey from Pakistan.**

Public Health Action. 2021 Sep 21;11(3):114-119. doi: 10.5588/pha.20.0077.

Abbas S(1), Denholm J(2), Kermode M(1), Xiaoguang Y(3), Kane S(1).

OBJECTIVE: To describe and quantify patients' self-reported experiences of receiving healthcare from Pakistan's Programmatic Management of Drug-Resistant Tuberculosis (PMDT) model of care, and to understand these experiences within the broader context of Pakistan's health system.
METHOD: This was a cross-sectional survey of patients attending three PMDT clinics in Khyber-Pakhtunkhwa Province in Pakistan.
RESULTS: The median consultation time at the PMDT clinics was 10 minutes. In their most recent visit to the PMDT clinic, 34.9% of patients spent >40% of their monthly income to access treatment. To specify, 71% of patients reported spending out-of-pocket for ancillary medicines and 44.7% for laboratory tests. In 10.5% of cases, medicines for drug-resistant TB (DR-TB) were dispensed without the patient attending the clinic. Only 43.7% of treatment supporters regularly accompanied patients to the clinic, and 6% supervised the patient's intake of medicines. Disbursement of financial support was irregular in 98.6% of cases. Only 6.2% of patients received their daily injections from a public facility, the rest went elsewhere.
CONCLUSION: Several shortcomings in PMDT services, including hurried consultations, irregularities in financial support, and gaps in Pakistan's broader health system undermined healthcare experience of patients with DR-TB. To improve health outcomes and patients' care experience these service gaps need to be addressed.

DOI: 10.5588/pha.20.0077
PMCID: PMC8455020
PMID: 34567986

13. **High resolution melting assay as a reliable method for diagnosing drug-resistant TB cases: a systematic review and meta-analysis.**

BMC Infect Dis. 2021 Sep 22;21(1):989. doi: 10.1186/s12879-021-06708-1.

Keikha M(1)(2), Karbalaei M(3).

BACKGROUND: Tuberculosis (TB) is one of the most contagious infectious diseases worldwide. Currently, drug-resistant Mycobacterium tuberculosis (Mtb) isolates are considered as one of the main challenges in the global TB control strategy. Rapid detection of resistant strains effectively reduces morbidity and mortality of world's population. Although both culture and conventional antibiotic susceptibility testing are time-consuming, recent studies have shown that high resolution melting (HRM) assay can be used to determine the types of antibiotic resistance. In the present meta-analysis, we evaluated the discriminative power of HRM in detecting all drug-resistance cases of TB.
METHODS: A systematic search was performed using databases such as Cochrane Library, Scopus, PubMed, Web of Science, and Google Scholar. Related studies on the effect of HRM in the diagnosis of drug-resistant (DR) TB cases were retrieved by April 2021. We used Meta-Disc software to evaluate the pooled diagnostic sensitivity and specificity of HRM for the detection of each type of drug-resistant cases. Finally, diagnostic value of HRM was characterized by summary receiver operating characteristic (SROC) curve and the area under the curve (AUC) method.
RESULTS: Overall 47 studies (4,732 Mtb isolates) met our criteria and were included in the present meta-analysis. Sensitivity, specificity, and AUC of HRM were measured for antibiotics such as isoniazid (93%, 98%, 0.987), rifampin (94%, 97%, 0963), ethambutol (82%, 87%, 0.728), streptomycin (82%, 95%, 0.957), pyrazinamide (72%, 84%, 0.845), fluoroquinolones (86%, 99%, 0.997), MDR-TB (90%, 98%, 0.989), and pan-drug-resistant TB (89%, 95%, 0.973).
CONCLUSIONS: The HRM assay has high accuracy for the identification of drug-resistant TB, particularly firs-line anti-TB drugs. Therefore, this method is considered as an alternative option for the rapid diagnosis of DR-TB cases. However, due to heterogeneity of included studies, the results of HRM assays should be interpreted based on conventional drug susceptibility testing.

DOI: 10.1186/s12879-021-06708-1
PMCID: PMC8456628
PMID: 34551717 [Indexed for MEDLINE]

14. **Exposure-safety analysis of QTc interval and transaminase levels following bedaquiline administration in patients with drug-resistant tuberculosis.**

CPT Pharmacometrics Syst Pharmacol. 2021 Oct 9. doi: 10.1002/psp4.12722. Online ahead of print.

Tanneau L(1), Svensson EM(1)(2), Rossenu S(3), Karlsson MO(1).

Bedaquiline (BDQ) has shown great value in the treatment of multidrug-resistant tuberculosis (MDR-TB) in recent years. However, exposure-safety relationships must be explored to extend the use of BDQ. Two reported safety findings for BDQ are prolongation of the QTc interval and elevation of transaminase levels. In this study, we investigated the potential relationships between BDQ and/or its main metabolite (M2) pharmacokinetic (PK) metrics and QTcF interval or transaminase levels, in MDR-TB patients using the approved dose regimen. Data from 429 MDR-TB patients from two phase IIb studies were analyzed via non-linear mixed-effects modeling. Individual model-predicted concentrations and summary PK metrics were evaluated respectively in the QTcF interval and transaminase levels exposure-response models. Investigation of further covariate effects was performed in both models. M2 concentrations were found to be responsible for the drug-related QTcF increase in a model accounting for circadian rhythm patterns, time on study, effect of concomitant medication with QT liability, and patient demographics. Simulations with the final model suggested that doses higher than the approved dose (leading to increased M2 concentrations) are not expected to lead to critical QTcF interval increase. No exposure-safety relationship could be described with transaminase levels, despite previous reports of higher levels in BDQ-treated patients. The developed longitudinal models characterized the role of M2 concentrations in QTc interval prolongation and found no concentration dependency for transaminase levels elevation, together suggesting that BDQ exposure at the high end of the observed range may not be associated with a higher risk of safety events.

DOI: 10.1002/psp4.12722
PMID: 34626526

15. **Insignificant difference in culture conversion between bedaquiline-containing and bedaquiline-free all-oral short regimens for multidrug-resistant tuberculosis.**

Int J Infect Dis. 2021 Oct;111:138-147. doi: 10.1016/j.ijid.2021.08.055. Epub 2021 Aug 25.

Fu L(1), Weng T(2), Sun F(2), Zhang P(1), Li H(1), Li Y(2), Yang Q(3), Cai Y(4), Zhang X(5), Liang H(6), Chen X(4), Wang Z(1), Liu L(7), Zhang W(8), Deng G(9).

BACKGROUND: Multidrug-resistant tuberculosis (MDR-TB) patients have been suffering long, ineffective, and toxic treatment until short-course injectable-free regimens emerged. However, the new WHO-recommended regimens

might be less feasible in the real-world setting. Here, we evaluated two optimized all-oral short-course regimens in China.
METHODS: From April 2019 to August 2020, we conducted a prospective nonrandomized controlled trial and consecutively included 103 MDR-TB patients diagnosed with pulmonary MDR-TB in Shenzhen, China. A 4-5 drug regimen of 9-12 months was tailored to the strain's resistance patterns, patients' affordability, and tolerance to drugs. This was an interim analysis, focusing on the early treatment period.
RESULTS: 53.4% (55/103) of patients were prescribed linezolid, fluoroquinolone (FQ), clofazimine, cycloserine, and pyrazinamide, followed by a regimen in which clofazimine was replaced by bedaquiline (35/103, 34.0%). The culture conversion rate was 83.1% and 94.4% at two and four months, respectively, with no significant difference between bedaquiline-free and bedaquiline-containing cases and between FQ-susceptible and FQ-resistant cases. Among 41 patients who completed treatment, 40 (97.6%) patients had a favorable outcome and no relapse was observed. Peripheral neuropathy and arthralgia/myalgia were the most frequent AEs (56.3%, 58/103). 18 AEs caused permanent discontinuation of drugs, mostly due to pyrazinamide and linezolid.
CONCLUSION: Optimized all-oral short-course regimens showed satisfactory efficacy and safety in early treatment stage. Further research is needed to confirm these results.

DOI: 10.1016/j.ijid.2021.08.055
PMID: 34454119 [Indexed for MEDLINE]

16. **Scale-up and impact of digital and molecular diagnostic technologies on TB diagnosis and timely linkage to care in Tajikistan.**

J Infect Dev Ctries. 2021 Sep 29;15(9.1):58S-65S. doi: 10.3855/jidc.13758.

Khushvakhtov S(1), Davtyan H(2), Alaverdyan S(2), Harries A(3), Kabirov O(4), Azamova S(5), Sharipova F(5), Sattorov S(6), Rajabov A(5).

INTRODUCTION: Tajikistan is scaling up molecular diagnostic and digital technologies to strengthen its fight against drug-resistant TB (DR-TB). The study aimed to document national scale-up GeneXpert/GxAlert and Open MRS from 2012-2019 and compare time taken from TB diagnosis to treatment and quality of data recording before and after the introduction of GxAlert.
METHODOLOGY: This was a longitudinal study that included a comparison of historical cohorts. Continuous variables were compared using Wilcoxon Rank-Sum test and categorical variables using the chi square test.
RESULTS: GeneXpert was introduced in 2011 and scaled up to 46 instruments in 43

(51%) diagnostic laboratories by May 2019. GxAlert was introduced in August 2018 and connected with all GeneXpert instruments by February 2019. Open MRS was introduced in 2014 and implemented in all 108 treatment centers by mid-2018. Time from diagnosis to treatment pre-GxAlert (range 0-749, median 3, days) was significantly longer than with GxAlert (range 0-273, median 3, days) ($p < 0.001$). The proportion of patients whose time from diagnosis to treatment was > 2 weeks was 16% (282/1740) pre-GxAlert and 11% (206/1902) with GxAlert ($p < 0.001$). Between 31%-34% of patients with DR-TB results in Open MRS did not have results available in GeneXpert/GxAlert systems. Where results were present in both systems, there were discrepancies in 8.2% of patients pre-GxAlert and 4.3% with GxAlert ($p = 0.25$).
CONCLUSIONS: The scale-up of GeneXpert and digital technologies in Tajikistan was associated with a reduction in the proportion of patients with delays more than 2 weeks between diagnosis and treatment, but data quality recording improved only slightly.

DOI: 10.3855/jidc.13758
PMID: 34609961

17. **Population pharmacokinetics and target attainment analysis of linezolid in multidrug-resistant tuberculosis patients.**

Br J Clin Pharmacol. 2021 Oct 7. doi: 10.1111/bcp.15102. Online ahead of print.

Tietjen AK(1)(2), Kroemer N(1), Cattaneo D(3), Baldelli S(3), Wicha SG(1).

AIM: This study investigates the pharmacokinetic/pharmacodynamic (PK/PD) target attainment of linezolid in patients infected with multidrug-resistant (MDR) tuberculosis (TB).
METHODS: A pharmacometric model was developed including 244 timed linezolid concentration samples from 39 patients employing NONMEM® 7.4. The probability of target attainment (PTA, PK/PD target: fAUC/MIC of 119) as well as a region-specific cumulative fraction of response (CFR) were estimated for different dosing regimens.
RESULTS: A one-compartment model with linear elimination with a clearance (CL) of 7.69 L/h (Interindividual variability (IIV): 34.1%), a volume of distribution (Vd) of 45.2 L and an absorption constant (KA) of 0.679 h-1 (Interoccasion variability: 143.7%) allometric scaled by weight best described the PK of linezolid. The PTA at a minimal inhibitory concentration (MIC) of 0.5 mg/L was

55% or 97% if patients receiving 300 mg or 600 mg twice daily, respectively. CFRs varied greatly among populations and geographic regions. A desirable global CFR of ≥90% was achieved if linezolid was administered at a dose of 600 mg twice daily but not at a dose of 300 mg twice daily.
CONCLUSION: This study showed that a dose of 300 mg twice daily of linezolid might not be sufficient to treat MDR-TB patients from a PK/PD perspective. Thus, it might be recommendable to start with a higher dose of 600 mg twice daily to ensure PK/PD target attainment. Hereby, therapeutic drug monitoring (TDM) and MIC determination should be performed to control PK/PD target attainment as linezolid shows high variability in its PK in the TB population.

DOI: 10.1111/bcp.15102
PMID: 34622478

18. **Xpert MTB/XDR for rapid detection of drug-resistant tuberculosis beyond rifampicin.**

Lancet Infect Dis. 2021 Oct 7:S1473-3099(21)00481-3. doi: 10.1016/S1473-3099(21)00481-3. Online ahead of print.

Mvelase NR(1), Mlisana KP(2).

DOI: 10.1016/S1473-3099(21)00481-3
PMID: 34627495

19. **'It has become everybody's business and nobody's business': Policy actor perspectives on the implementation of TB infection prevention and control (IPC) policies in South African public sector primary care health facilities.**

Glob Public Health. 2021 Oct;16(10):1631-1644. doi: 10.1080/17441692.2020.1839932. Epub 2020 Nov 8.

Colvin CJ(1)(2)(3), Kallon II(1), Swartz A(1)(3), MacGregor H(4), Kielmann K(5), Grant AD(6)(7)(8).

South Africa is increasingly offering screening, diagnosis and treatment of tuberculosis (TB), and especially drug-resistant TB, at the primary care level. Nosocomial transmission of TB within primary health facilities is a growing concern in South Africa, and globally. We explore here how TB infection prevention and control (IPC) policies, historically focused on hospitals, are

being implemented within primary care facilities. We spoke to 15 policy actors using in-depth interviews about barriers to effective TB-IPC and opportunities for improving implementation. We identified four drivers of poor policy implementation: fragmentation of institutional responsibility and accountability for TB-IPC; struggles by TB-IPC advocates to frame TB-IPC as an urgent and addressable policy problem; barriers to policy innovation from both a lack of evidence as well as a policy environment dependent on 'new' evidence to justify new policy; and the impact of professional medical cultures on the accurate recognition of and response to TB risks. Participants also identified examples of TB-IPC innovation and described conditions necessary for these successes. TB-IPC is a long-standing, complex health systems challenge. As important as downstream practices like mask-wearing and ventilation are, sustained, effective TB-IPC ultimately requires that we better address the upstream barriers to TB-IPC policy formulation and implementation.

DOI: 10.1080/17441692.2020.1839932
PMID: 33161838

20. **High rates of culture conversion and low loss to follow-up in MDR-TB patients managed at Regional Referral Hospitals in Uganda.**

BMC Infect Dis. 2021 Oct 12;21(1):1060. doi: 10.1186/s12879-021-06743-y.

Martin MK(1)(2), Paul OJ(3), Sara R(4), Hilary A(3), Frank M(5), Augustin MK(3), Stavia T(5), Christopher W(3), van Zanten TV(4), Gladys T(3).

BACKGROUND: Multi-drug resistant-tuberculosis (MDR-TB) is an emerging public health concern in Uganda. Prior to 2013, MDR-TB treatment in Uganda was only provided at the national referral hospital and two private-not-for profit clinics. From 2013, it was scaled up to seven regional referral hospitals (RRH). The aim of this study was to measure interim (6 months) treatment outcomes among the first cohort of patients started on MDR-TB treatment at the RRH in Uganda.
METHODS: This was a cross-sectional study in which a descriptive analysis of data collected retrospectively on a cohort of 69 patients started on MDR-TB treatment at six of the seven RRH between 1st April 2013 and 30th June 2014 and had been on treatment for at least 9 months was conducted.
RESULTS: Of the 69 patients, 21 (30.4%) were female, 39 (56.5%) HIV-negative, 30 (43.5%) resistant to both isoniazid and rifampicin and 57 (82.6%) category 1 or 2 drug susceptible TB treatment failures. Median age at start of treatment was 35 years (Interquartile range (IQR): 27-45), median time-to-treatment initiation was 27.5 (IQR: 6-89) days and of the 30 HIV-positive patients, 27 (90.0%) were on anti-retroviral treatment with a median CD4 count of 206 cells/microliter of blood (IQR: 113-364.5). Within 6 months of treatment, 59 (85.5%) patients

culture converted, of which 45 (65.2%) converted by the second month and the other 14 (20.3%) by the sixth month; one (1.5%) did not culture convert; three (4.4%) died; and six (8.8%) were lost-to-follow up. Fifty (76.8%) patients experienced at least one drug adverse event, while 40 (67.8%) gained weight. Mean weight gained was 4.7 (standard deviation: 3.2) kilograms.
CONCLUSIONS: Despite MDR-TB treatment initiation delays, most patients had favourable interim treatment outcomes with majority culture converting early and very few getting lost to follow-up. These encouraging interim outcomes indicate the potential for success of a scale-up of MDR-TB treatment to RRH.

DOI: 10.1186/s12879-021-06743-y
PMID: 34641816 [Indexed for MEDLINE]

21. **Novel mutations detected from drug resistant Mycobacterium tuberculosis isolated from North East of Thailand.**

World J Microbiol Biotechnol. 2021 Oct 13;37(11):194. doi: 10.1007/s11274-021-03163-7.

Thwe EP(1)(2), Namwat W(3), Pinlaor P(2)(4), Rueangsak K(5), Sangka A(6)(7)(8).

The emergence of drug-resistant tuberculosis is a major global public health threat. Thailand is one of the top 14 countries with high tuberculosis and multi-drug resistant tuberculosis rates. Immediate detection of drug-resistant tuberculosis is necessary to reduce mortality and morbidity by effectively providing treatment to ameliorate the formation of resistant strains. Limited data exist of mutation profiles in Northeastern Thailand. Here, 65 drug-resistant Mycobacterium tuberculosis isolates were used to detect mutations by polymerase chain reaction (PCR) and DNA sequencing. In the katG gene, mutations were occurred in 47 (79.7%) among 59 isoniazid resistant samples. For rpoB gene, 31 (96.9%) were observed as mutations in 32 rifampicin resistant isolates. Of 47 katG mutation samples, 45 (95.7%) had mutations in katG315 codon and 2 (4.3%) showed novel mutations at katG365 with amino acid substitution of CCG-CGG (Pro-Arg). Moreover, out of 31 rpoB mutation isolates, the codon positions rpoB516, rpoB526, rpoB531 and rpoB533 were 3 (9.7%), 8 (25.8%), 11 (35.5%) and 1 (3.2%), respectively. Seven isolates of double point mutation were found [rpoB516, 526; 1 (3.2%) and rpoB516, 531; 6 (19.4%)]. In addition, 1 (3.2%) sample had triple point mutation at codon positions rpoB516, 526 and 531. Common and novel mutation codons of the rpoB and katG genes were generated. Although DNA sequencing showed high accuracy, conventional PCR could be applied as an initial marker for screening drug-resistant Mycobacterium tuberculosis

isolates in limit resources region. Mutations reported here should be considered when developing new molecular diagnostic methods for implementation in Northeastern Thailand.

DOI: 10.1007/s11274-021-03163-7
PMID: 34642828

22. **Hear us! Accounts of people treated with injectables for drug-resistant TB.**

Public Health Action. 2021 Sep 21;11(3):146-154. doi: 10.5588/pha.21.0031.

Almeida A(1), Adjuntsov M(2), Bushura W(2), Delgado E(2), Drasher M(3), Fernando-Pancho M(2), Gasane M(2), Ianoşi MV(2), Lessem E(1), Musah A(2), Răduţ Ş(2), Sánchez Ríos CH(2), Soe KS(2), Venkatesan N(2), Villegas VV(2), Stillo J(3).

BACKGROUND: WHO drug-resistant TB (DR-TB) treatment recommendations now emphasize all-oral regimens, recommending against certain injectable agents and deprioritizing others due to inferior safety and efficacy. Despite increasing focus on patient-centered care, we are not aware of systematic attempts to qualitatively document patients' perspectives on injectable agents. This may inform implementation of WHO guidelines, emphasizing the importance of consultation with affected communities.
METHODS: Testimonies were provided by TB survivors who experienced hearing loss from treatment with injectable agents. Testimonies were submitted in writing in response to minimal, standardized, open-ended prompts. Participants provided a signed consent form (with options to participate anonymously or as a named co-author), and later gave input into the overall shape and recommendations of the article.
RESULTS: Fourteen TB survivors in 12 countries contributed testimonies. The following common themes emerged: lack of access to appropriate testing, information, treatment, or a collaborative treatment environment; the power of supportive care and social environments; stigma and isolation from TB treatment itself and resultant disability; and inaccessibility of cochlear implants.
CONCLUSIONS: Survivor testimonies indicate strong preferences for avoidance of injectable agents, supporting rapid implementation of revised WHO guidelines, as well as for quality and supportive care for both TB and disabilities.

DOI: 10.5588/pha.21.0031

PMCID: PMC8455027
PMID: 34567991

23. **A review on Coumarin derivatives as potent anti-Tuberculosis agent.**

Mini Rev Med Chem. 2021 Sep 27. doi: 10.2174/1389557521666210927124511. Online ahead of print.

Samar M(1), Kuldeep S(1), Bhoomika Y(2), Vaseem A(1), Shweta S(3).

BACKGROUND: Tuberculosis (TB) is an acute or chronic infectious disease caused by several species of Myco-bacterium, collectively called as tubercle bacilli or Mycobacterium tuberculosis complex. Around 10 million people get sick with tuberculosis (TB) each year. TB is the second leading cause of deaths today after HIV/AIDS. A serious problem in the context of MDR-TB, is the extensively drug-resistant TB which is an im-portant reason for the restricted chemotherapy in TB. Therefore, there is a need to explore new antitubercular (anti-TB) agents. Coumarin is an oxygen-containing heterocyclic compound and can be widely found in many natural products, and many of them display diverse biological activities.The wide spectrum of activities of coumarin molecules have intrigued the scientists to explore the natural coumarins and their synthetic deriva-tives for their potential as anti-TB drugs.
OBJECTIVE: The objective of this review is to emphasize on important coumarin analogs with anti-TB activities and their structure-activity relationships (SAR) for designing better anti-TB agents.
METHOD: Latest, authentic and published reports on various synthetic and natural coumarin derivatives and their anti-TB activities is being thoroughly studied and analyzed. The structural requirements of coumarins as anti-TB drugs have also been studied.
RESULT: Collection and compilation of reports on various synthetic and natural coumarin derivatives and their anti-TB activities is being done.
CONCLUSION: The study provides latest report on coumarin derivatives synthesized as anti-TB agent and wheth-er their activity depends on structural changes or not.

DOI: 10.2174/1389557521666210927124511
PMID: 34579635

24. **Ethionamide population pharmacokinetics/pharmacodynamics and therapeutic**

implications in South African adult patients with drug-resistant tuberculosis.

Br J Clin Pharmacol. 2021 Oct;87(10):3863-3870. doi: 10.1111/bcp.14795. Epub 2021 Mar 10.

Mugabo P(1), Mulubwa M(1).

INTRODUCTION: Ethionamide is part of the drug-resistant tuberculosis regimen whose pharmacokinetic (PK) and pharmacodynamic (PD) information is limited. The aim of the study was to describe the PK and simulate doses to assess PD attainment.
METHODS: This was an observational population PK study of patients admitted for drug-resistant tuberculosis at a hospital in South Africa. Nonlinear mixed-effects modelling implemented in Monolix 2019R2 was used to estimate population pharmacokinetic parameters. We performed Monte Carlo simulations to assess and optimise the dose regimen. The target Cmax range was 2.5-5 µg/mL, which is within the minimum inhibitory concentration (MIC) range. The target AUC0-24h was 140.5 µg*h/mL, which corresponds to the PK/PD target ratio AUC0-24h /MIC of 56.2.
RESULTS: A one-compartment pharmacokinetic model with a lag-time, first-order absorption and elimination best described the PK of ethionamide. The lag-time, absorption rate constant (ka), volume of distribution (V/F) and clearance (Cl/F) were 0.66 hours, 0.434 h-1 , 180 L and 99.5 L/h, respectively, for a typical individual weighing 52.6 kg. Between-subject variability in lag-time, ka, V/F and Cl/F were 38%, 92%, 168% and 120%, respectively. Simulation of the recommended doses of 15-20 mg/kg, 500 mg, 750 mg and 1000 mg for patients in the weight bands <33, 33-50, 51-70 and >70 kg resulted in <17% and 3% of the patients achieving the target Cmax and AUC0-24h , respectively.
CONCLUSION: There is high variability in ethionamide PK and very few patients attain the desired target exposure at standard or optimised doses. We propose individualised dose regimen optimisation.

DOI: 10.1111/bcp.14795
PMID: 33620754

25. **Brazilian cohort study of risk factors associated with unsuccessful outcomes of drug resistant tuberculosis.**

BMC Infect Dis. 2021 Oct 9;21(1):1049. doi: 10.1186/s12879-021-06756-7.

Bartholomay P(1)(2), Pinheiro RS(3), Dockhorn F(4), Pelissari DM(4), de Araújo

WN(5)(6).

BACKGROUND: Treatment outcomes were evaluated of a cohort of new pulmonary tuberculosis (TB) cases that were rifampicin resistant, multidrug-resistant, or extensively resistant during 2013 and 2014 in Brazil. The objective of this study is to identify factors associated with unfavorable treatment outcomes for drug-resistant TB cases.
METHODS: The Brazilian Special Tuberculosis Treatment Information System (SITE-TB) was the main data source. The independent variables were classified into four blocks (block I: individual characteristics; block II: clinical characteristics and proposed treatment; block III: treatment follow-up characteristics; and block IV: TB history). The category of successful therapeutic outcome was compared with lost to follow-up, failure, and death. Considering the multiple outcomes as the dependent variable, the odds ratios (OR) and its respective 95% confidence interval (95% CI) were estimated by multinomial logistic regression.
RESULTS: After applying the exclusion criteria, 980 (98.8%) individuals were included in the study. Of these, 621 (63.4%) had successful treatment, 163 (16.6%) lost to follow-up, 76 (7.8%) failed, and 120 (12.2%) died. Important factors associated with lost to follow-up in the final model included use of illicit drugs (OR = 2.5 95% CI: 1.57-3.82). Outcome failure was associated with having disease in both lungs (OR = 2.0; 95% CI: 1.09-3.62) and using more than one or not using injectable medication (OR = 2.8; 95% CI: 1.05-7.69). Major factors for the death outcome were at least 60 years old (OR = 3.4; 95% CI: 1.90-6.03) and HIV positive (OR = 2.7; 95% CI: 1.45-4.83).
CONCLUSIONS: The factors associated with unfavorable treatment outcomes were different. Some of these factors are specific to each outcome, which reflects the complexity of providing care to these individuals.

DOI: 10.1186/s12879-021-06756-7
PMID: 34627179 [Indexed for MEDLINE]

26. **Proposed linezolid dosing strategies to minimize adverse events for treatment of extensively drug-resistant tuberculosis.**

Clin Infect Dis. 2021 Oct 4:ciab699. doi: 10.1093/cid/ciab699. Online ahead of print.

Imperial MZ(1), Nedelman JR(2), Conradie F(3), Savic RM(1).

BACKGROUND: We evaluated clinical trial data (Nix-TB, NCT02333799) to provide

data-driven dosing recommendations to potentially minimize linezolid toxicity in patients with extensively drug-resistant tuberculosis.
METHODS: Based on 104 participants, a pharmacokinetic model and toxicodynamic models for peripheral neuropathy, hemoglobin, and platelets were developed. Simulations compared safety outcomes for daily linezolid of 1200 and 600 mg, with and without dose adjustments for toxicity. Severe neuropathy was based on symptom scores from the Brief Peripheral Neuropathy Screen. Severe anemia and thrombocytopenia were defined as ≥grade 3 adverse events according to the Division of Microbiology and Infectious Disease Adult Toxicity table.
RESULTS: Predicted individual concentration-time profiles were a major predictor in all three toxicodynamic models. Simulations showed higher percentages of patients with severe neuropathy (median: 19% (90%CI: 17-22%) vs 5% (4-7%)) and severe anemia (15% (12-17%) vs 1% (0-2%)) between 1200 and 600 mg daily linezolid. No differences in severe thrombocytopenia were observed (median: <1% for both daily doses). Generally, neuropathy occurred after 3 to 6 months of treatment and, with protocol-specified management, reversed within 15 months after onset. Simulations indicated that a >10% decrease from pretreatment in hemoglobin level after 4 weeks of treatment would have maximum sensitivity (82%) and specificity (84%) for predicting severe anemia. Reducing dose from 1200 to 600 mg triggered by this marker may prevent 60% (90%CI: 45-72) of severe anemia.
CONCLUSIONS: Simple neuropathy symptom and hemoglobin monitoring may guide linezolid dosing to avoid toxicities, but prospective testing is needed to confirm benefit-to-risk ratio.

DOI: 10.1093/cid/ciab699
PMID: 34604901

27. **Optima TB: A tool to help optimally allocate tuberculosis spending.**

PLoS Comput Biol. 2021 Sep 27;17(9):e1009255. doi: 10.1371/journal.pcbi.1009255. eCollection 2021 Sep.

Goscé L(1), Abou Jaoude GJ(1), Kedziora DJ(2), Benedikt C(3), Hussain A(2), Jarvis S(2), Skrahina A(4), Klimuk D(4), Hurevich H(4), Zhao F(3), Fraser-Hurt N(3), Cheikh N(3), Gorgens M(3), Wilson DJ(3), Abeysuriya R(2), Martin-Hughes R(2), Kelly SL(2), Roberts A(2), Stuart RM(2)(5), Palmer T(1), Panovska-Griffiths J(1)(6), Kerr CC(2), Wilson DP(2), Haghparast-Bidgoli H(1), Skordis J(1), Abubakar I(1).

Approximately 85% of tuberculosis (TB) related deaths occur in low- and

middle-income countries where health resources are scarce. Effective priority setting is required to maximise the impact of limited budgets. The Optima TB tool has been developed to support analytical capacity and inform evidence-based priority setting processes for TB health benefits package design. This paper outlines the Optima TB framework and how it was applied in Belarus, an upper-middle income country in Eastern Europe with a relatively high burden of TB. Optima TB is a population-based disease transmission model, with programmatic cost functions and an optimisation algorithm. Modelled populations include age-differentiated general populations and higher-risk populations such as people living with HIV. Populations and prospective interventions are defined in consultation with local stakeholders. In partnership with the latter, demographic, epidemiological, programmatic, as well as cost and spending data for these populations and interventions are then collated. An optimisation analysis of TB spending was conducted in Belarus, using program objectives and constraints defined in collaboration with local stakeholders, which included experts, decision makers, funders and organisations involved in service delivery, support and technical assistance. These analyses show that it is possible to improve health impact by redistributing current TB spending in Belarus. Specifically, shifting funding from inpatient- to outpatient-focused care models, and from mass screening to active case finding strategies, could reduce TB prevalence and mortality by up to 45% and 50%, respectively, by 2035. In addition, an optimised allocation of TB spending could lead to a reduction in drug-resistant TB infections by 40% over this period. This would support progress towards national TB targets without additional financial resources. The case study in Belarus demonstrates how reallocations of spending across existing and new interventions could have a substantial impact on TB outcomes. This highlights the potential for Optima TB and similar modelling tools to support evidence-based priority setting.

DOI: 10.1371/journal.pcbi.1009255
PMCID: PMC8496838
PMID: 34570767

28. **A recombinant selective drug-resistant M. bovis BCG enhances the bactericidal activity of a second-line anti-tuberculosis regimen.**

Biomed Pharmacother. 2021 Oct;142:112047. doi: 10.1016/j.biopha.2021.112047. Epub 2021 Aug 21.

Chiwala G(1), Liu Z(2), Mugweru JN(3), Wang B(4), Khan SA(5), Bate PNN(1), Yusuf B(1), Hameed HMA(1), Fang C(1), Tan Y(6), Guan P(6), Hu J(6), Tan S(6), Liu J(6), Zhong N(7), Zhang T(8).

Drug-resistant tuberculosis (DR-TB) poses a new threat to global health; to improve the treatment outcome, therapeutic vaccines are considered the best chemotherapy adjuvants. Unfortunately, there is no therapeutic vaccine approved against DR-TB. Our study assessed the therapeutic efficacy of a recombinant drug-resistant BCG (RdrBCG) vaccine in DR-TB. We constructed the RdrBCG overexpressing Ag85B and Rv2628 by selecting drug-resistant BCG strains and transformed them with plasmid pEBCG or pIBCG to create RdrBCG-E and RdrBCG-I respectively. Following successful stability testing, we tested the vaccine's safety in severe combined immune deficient (SCID) mice that lack both T and B lymphocytes plus immunoglobulins. Finally, we evaluated the RdrBCG's therapeutic efficacy in BALB/c mice infected with rifampin-resistant M. tuberculosis and treated with a second-line anti-TB regimen. We obtained M. bovis strains which were resistant to several second-line drugs and M. tuberculosis resistant to rifampin. Notably, the exogenously inserted genes were lost in RdrBCG-E but remained stable in the RdrBCG-I both in vitro and in vivo. When administered adjunct to a second-line anti-TB regimen in a murine model of DR-TB, the RdrBCG-I lowered lung M. tuberculosis burden by 1 log10. Furthermore, vaccination with RdrBCG-I adjunct to chemotherapy minimized lung tissue pathology in mice. Most importantly, the RdrBCG-I showed almost the same virulence as its parent BCG Tice strain in SCID mice. Our findings suggested that the RdrBCG-I was stable, safe and effective as a therapeutic vaccine. Hence, the "recombinant" plus "drug-resistant" BCG strategy could be a useful concept for developing therapeutic vaccines against DR-TB.

DOI: 10.1016/j.biopha.2021.112047
PMID: 34426260

29. **Risk factors for poor engagement in drug-resistant TB care in South Africa: a systematic review.**

Public Health Action. 2021 Sep 21;11(3):139-145. doi: 10.5588/pha.21.0007.

McNabb KC(1), Bergman A(1), Farley JE(1)(2).

BACKGROUND: Metrics of poor patient engagement, including missed appointments, treatment interruption, sub-optimal medication adherence, and loss to follow-up, have been linked to poor clinical multidrug-resistant TB (MDR-TB) outcomes. Understanding the risk factors for poor patient engagement is necessary to improve outcomes and control TB. This review synthesizes the risk factors for poor patient engagement in MDR-TB treatment across South Africa.

DESIGN: A systematic review of five databases (PubMed, Embase, CINAHL, Cochrane, and Web of Science) was conducted, covering articles published between 2010 and 2020. Articles were included if they provided information about risk factors associated with poor engagement among adults (⩾15 years) in treatment for MDR-TB in South Africa. Reviews, editorials, abstracts, and case studies were excluded.
RESULTS: Six studies met the inclusion criteria. Male sex and younger age were the most consistently identified risk factors for poor engagement; however, there was a lack of consistency in the choice of covariates, measurement of the variables, analytic methods, and significant factors associated with poor engagement between studies. Alcohol use, substance use, living with HIV, pulmonary TB site, and ethnicity were all identified as risk factors in at least one included study, while formal housing and steady employment were found to be protective.
CONCLUSION: The available literature offers little cohesive data to address poor patient engagement in this population. Further research needs to focus on identifying and addressing risk factors for poor patient engagement. This is particularly salient within the context of newer all-oral and short-course MDR-TB treatment regimens.

DOI: 10.5588/pha.21.0007
PMCID: PMC8455023
PMID: 34567990

30. **Catastrophic costs among tuberculosis-affected households in Zimbabwe: A national health facility-based survey.**

Trop Med Int Health. 2021 Oct;26(10):1248-1255. doi: 10.1111/tmi.13647. Epub 2021 Aug 3.

Timire C(1)(2)(3), Ngwenya M(4), Chirenda J(5), Metcalfe JZ(6), Kranzer K(3), Pedrazzoli D(7)(8), Takarinda KC(1)(2), Nguhiu P(9), Madzingaidzo G(1), Ndlovu K(1), Mapuranga T(1), Cornell M(10), Sandy C(1).

OBJECTIVES: To determine the incidence and major drivers of catastrophic costs among TB-affected households in Zimbabwe.
METHODS: We conducted a nationally representative health facility-based survey with random cluster sampling among consecutively enrolled drug-susceptible (DS-TB) and drug-resistant TB (DR-TB) patients. Costs incurred and income lost due to TB illness were captured using an interviewer-administered standardised questionnaire. We used multivariable logistic regression to determine the risk factors for experiencing catastrophic costs.

RESULTS: A total of 841 patients were enrolled and were weighted to 900 during data analysis. There were 500 (56%) males and 46 (6%) DR-TB patients. Thirty-five (72%) DR-TB patients were HIV co-infected. Overall, 80% (95% CI: 77-82) of TB patients and their households experienced catastrophic costs. The major cost driver pre-TB diagnosis was direct medical costs. Nutritional supplements were the major cost driver post-TB diagnosis, with a median cost of US$360 (IQR: 240-600). Post-TB median diagnosis costs were three times higher among DR-TB (US$1,659 [653-2,787]) than drug DS-TB-affected households (US$537 [204-1,134]). Income loss was five times higher among DR-TB than DS-TB patients. In multivariable analysis, household wealth was the only covariate that remained significantly associated with catastrophic costs: The poorest households had 16 times the odds of incurring catastrophic costs versus the wealthiest households (adjusted odds ratio [aOR: 15.7 95% CI: 7.5-33.1]).
CONCLUSION: The majority of TB-affected households, especially those affected by DR-TB, experienced catastrophic costs. Since the major cost drivers fall outside the healthcare system, multi-sectoral approaches to TB control and linking TB patients to social protection may reduce catastrophic costs.

DOI: 10.1111/tmi.13647
PMCID: PMC8519355
PMID: 34192392

31. **Treatment success using novel and adapted treatment regimens in registered DR-TB children in Dushanbe, Tajikistan, 2013-2019.**

J Infect Dev Ctries. 2021 Sep 29;15(9.1):7S-16S. doi: 10.3855/jidc.14798.

Pirmahmadzoda B(1), Hann K(2), Akopyan K(3), Grigoryan R(4), Geliukh E(5), Hushvaht S(6), Surayo O(1), Tilloeva Z(1).

INTRODUCTION: Approximately 3% of all pediatric TB cases develop MDR-TB, with only 3-4% of such children receiving MDR-TB treatment. In Tajikistan, children as a proportion of all DR-TB in the country increased from 4.3 to 7.5% during 2013-2018. Despite limited evidence on the use of new anti-TB drugs in children, WHO has updated its guidelines for DR-TB treatment for children, and Tajikistan did so in 2013 and 2017. Novel and adapted regimens included individual regimens for RR/MDR, XDR (with and without Bedaquiline and Delamanid) and short treatment regimens with and without injectables. It is important to document the outcomes of the treatment regimens. Therefore, the aim of this study was to describe characteristics of children receiving different treatment regimens for DR-TB, the culture conversion and treatment outcomes.

METHODOLOGY: Cohort study of children enrolled in DR-TB treatment by the National Tuberculosis Program in Dushanbe, Tajikistan, January 2013 to July 2019.
RESULTS: The study included 60 DR-TB children. The male to female ratio was 1:2 and mean age 13.6 years. Median time to culture conversion was 66 days [IQR:31-103; Range:2-232]. In children with treatment outcomes (N = 58), 93% had favorable outcomes. There were four children (7%) with unfavorable treatment outcomes, all of whom were female 15-17 years, on standard (RR/MDR) treatment during 2013-2015. Favorable outcomes by DR-TB type were 91%, 90%, and 100% in RR/MDR, PreXDR, and XDR-TB patients, respectively.
CONCLUSIONS: All children enrolled after the introduction of modified guidelines for novel and adapted regimens for DR-TB showed positive TB treatment outcomes.

DOI: 10.3855/jidc.14798
PMID: 34609955

32. **Potent anti-mycobacterial and immunomodulatory activity of some bioactive molecules of Indian ethnomedicinal plants that have the potential to enter in TB management.**

J Appl Microbiol. 2021 Oct;131(4):1578-1599. doi: 10.1111/jam.15088. Epub 2021 Apr 13.

Sarangi A(1), Das BS(1), Patnaik G(2), Sarkar S(3), Debnath M(4), Mohan M(5), Bhattacharya D(1).

Tuberculosis (TB) is one of the deadliest infectious diseases of human civilization. Approximately one-third of global population is latently infected with the TB pathogen Mycobacterium tuberculosis (M.tb). The discovery of anti-TB antibiotics leads to decline in death rate of TB. However, the evolution of antibiotic-resistant M.tb-strain and the resurgence of different immune-compromised diseases re-escalated the death rate of TB. WHO has already cautioned about the chances of pandemic situation in TB endemic countries until the discovery of new anti-tubercular drugs, that is, the need of the hour. Analysing the pathogenesis of TB, it was found that M.tb evades the host by altering the balance of immune response and affects either by killing the cells or by creating inflammation. In the pre-antibiotic era, traditional medicines were only therapeutic measures for different infectious diseases including tuberculosis. The ancient literatures of India or ample Indian traditional

knowledge and ethnomedicinal practices are evidence for the treatment of TB using different indigenous plants. However, in the light of modern scientific approach, anti-TB effects of those plants and their bioactive molecules were not established thoroughly. In this review, focus has been given on five bioactive molecules of different traditionally used Indian ethnomedicinal plants for treatment of TB or TB-like symptom. These compounds are also validated with proper identification and their mode of action with modern scientific approaches. The effectiveness of these molecules for sensitive or drug-resistant TB pathogen in clinical or preclinical studies was also evaluated. Thus, our specific aim is to highlight such scientifically validated bioactive compounds having anti-mycobacterial and immunomodulatory activity for future use as medicine or adjunct-therapeutic molecule for TB management.

DOI: 10.1111/jam.15088
PMID: 33772980 [Indexed for MEDLINE]

33. **Comparative efficacy of the novel diarylquinoline TBAJ-876 and bedaquiline against a resistant Rv0678 mutant in a mouse model of tuberculosis.**

Antimicrob Agents Chemother. 2021 Sep 27:AAC0141221. doi: 10.1128/AAC.01412-21. Online ahead of print.

Almeida D(1), Converse PJ(1), Li SY(1), Upton AM(2), Fotouhi N(2), Nuermberger EL(1)(3).

Bedaquiline (BDQ, B) is the first-in-class diarylquinoline to be approved for treatment of tuberculosis (TB). Recent guidelines recommend its use in treatment of multidrug- and extensively drug-resistant (MDR/XDR-TB). The newly approved regimen combining BDQ with pretomanid and linezolid is the first 6-month oral regimen proven to be effective against MDR/XDR-TB. However, the emergence of BDQ resistance, primarily due to inactivating mutations in the Rv0678 gene encoding a repressor of the MmpS5-MmpL5 transporter, threatens to undermine the efficacy of new BDQ-containing regimens. Since the shift in MIC due to these mutations is relatively small (2-to-8x), safer and more potent diarylquinoline analogues may be more effective than BDQ. TBAJ-876, which is in phase 1 trials, has more potent in vitro activity and a superior pre-clinical safety profile than BDQ. Using a murine model of TB, we evaluated the dose-dependent activity of TBAJ-876 compared to BDQ against the wild-type H37Rv strain and an isogenic Rv0678 loss-of-function mutant. Though the mutation affected the MIC of both drugs, the MIC of TBAJ-876 against the mutant was 10-fold lower than that of BDQ. TBAJ-876 at doses ≥6.25 mg/kg had greater efficacy against both strains compared to BDQ

at 25 mg/kg, when administered alone or in combination with pretomanid and linezolid. Likewise, no selective amplification of BDQ-resistant bacteria was observed at TBAJ-876 doses ≥6.25 mg/kg. These results indicate that replacing BDQ with TBAJ-876 may shorten the duration of TB treatment and be more effective in treating and preventing infections caused by Rv0678 mutants.

DOI: 10.1128/AAC.01412-21
PMID: 34570644

34. **The role of microbiota in respiratory health and diseases, particularly in tuberculosis.**

Biomed Pharmacother. 2021 Nov;143:112108. doi: 10.1016/j.biopha.2021.112108. Epub 2021 Sep 21.

Shah T(1), Shah Z(2), Baloch Z(3), Cui X(4).

Trillions of beneficial and hostile microorganisms live in the human respiratory and gastrointestinal tracts, which act as gatekeepers in maintaining human health, i.e., protecting the body from pathogens by colonizing mucosal surfaces with microbiota-derived antimicrobial metabolites such as short-chain fatty acids or host-derived cytokines and chemokines. It is widely accepted that the microbiome interacts with each other and with the host in a mutually beneficial relationship. Microbiota in the respiratory tract may also play a crucial role in immune homeostasis, maturation, and maintenance of respiratory physiology. Anti-TB antibiotics may cause dysbiosis in the lung and intestinal microbiota, affecting colonization resistance and making the host more susceptible to Mycobacterium tuberculosis (M. tuberculosis) infection. This review discusses recent advances in our understanding of the lung microbiota composition, the lungs and intestinal microbiota related to respiratory health and diseases, microbiome sequencing and analysis, the bloodstream, and the lymphatic system that underpin the gut-lung axis in M. tuberculosis-infected humans and animals. We also discuss the gut-lung axis interactions with the immune system, the role of the microbiome in TB pathogenesis, and the impact of anti-TB antibiotic therapy on the microbiota in animals, humans, and drug-resistant TB individuals.

DOI: 10.1016/j.biopha.2021.112108
PMID: 34560539

35. **Detection of isoniazid, fluoroquinolone, ethionamide, amikacin, kanamycin, and**

capreomycin resistance by the Xpert MTB/XDR assay: a cross-sectional multicentre diagnostic accuracy study.

Lancet Infect Dis. 2021 Oct 7:S1473-3099(21)00452-7. doi: 10.1016/S1473-3099(21)00452-7. Online ahead of print.

Penn-Nicholson A(1), Georghiou SB(2), Ciobanu N(3), Kazi M(4), Bhalla M(5), David A(6), Conradie F(6), Ruhwald M(2), Crudu V(3), Rodrigues C(4), Myneedu VP(5), Scott L(6), Denkinger CM(7), Schumacher SG(2); Xpert XDR Trial Consortium.

BACKGROUND: The WHO End TB Strategy requires drug susceptibility testing and treatment of all people with tuberculosis, but second-line diagnostic testing with line-probe assays needs to be done in experienced laboratories with advanced infrastructure. Fewer than half of people with drug-resistant tuberculosis receive appropriate treatment. We assessed the diagnostic accuracy of the rapid Xpert MTB/XDR automated molecular assay (Cepheid, Sunnyvale, CA, USA) to overcome these limitations.
METHODS: We did a prospective study involving individuals presenting with pulmonary tuberculosis symptoms and at least one risk factor for drug resistance in four sites in India (New Delhi and Mumbai), Moldova, and South Africa between July 31, 2019, and March 21, 2020. The Xpert MTB/XDR assay was used as a reflex test to detect resistance to isoniazid, fluoroquinolones, ethionamide, amikacin, kanamycin, and capreomycin in adults with positive results for Mycobacterium tuberculosis complex on Xpert MTB/RIF or Ultra (Cepheid). Diagnostic performance was assessed against a composite reference standard of phenotypic drug-susceptibility testing and whole-genome sequencing. This study is registered with ClinicalTrials.gov, number NCT03728725.
FINDINGS: Of 710 participants, 611 (86%) had results from both Xpert MTB/XDR and the reference standard for any drug and were included in analysis. Sensitivity for Xpert MTB/XDR detection of resistance was 94% (460 of 488, 95% CI 92-96) for isoniazid, 94% (222 of 235, 90-96%) for fluoroquinolones, 54% (178 of 328, 50-61) for ethionamide, 73% (60 of 82, 62-81) for amikacin, 86% (181 of 210, 81-91) for kanamycin, and 61% (53 of 87, 49-70) for capreomycin. Specificity was 98-100% for all drugs. Performance was equivalent to that of line-probe assays. The non-determinate rate of Xpert MTB/XDR (ie, invalid M tuberculosis complex detection) was 2·96%.
INTERPRETATION: The Xpert MTB/XDR assay showed high diagnostic accuracy and met WHO's minimum target product profile criteria for a next-generation drug susceptibility test. The assay has the potential to diagnose drug-resistant tuberculosis rapidly and accurately and enable optimum treatment.
FUNDING: German Federal Ministry of Education and Research through KfW, Dutch Ministry of Foreign Affairs, and Australian Department of Foreign Affairs and Trade.

DOI: 10.1016/S1473-3099(21)00452-7
PMID: 34627496

36. **Relationship between Plasma and Intracellular Concentrations of Bedaquiline and Its M2 Metabolite in South African Patients with Rifampin-Resistant Tuberculosis.**

Antimicrob Agents Chemother. 2021 Oct 18;65(11):e0239920. doi: 10.1128/AAC.02399-20. Epub 2021 Aug 9.

Ngwalero P(#)(1), Brust JCM(#)(2), van Beek SW(3), Wasserman S(4)(5), Maartens G(1)(4)(5), Meintjes G(4)(5), Joubert A(1), Norman J(1), Castel S(1), Gandhi NR(6), Denti P(1), McIlleron H(1)(4)(5), Svensson EM(3)(7), Wiesner L(1).

Bedaquiline is recommended for the treatment of all patients with rifampin-resistant tuberculosis (RR-TB). Bedaquiline accumulates within cells, but its intracellular pharmacokinetics have not been characterized, which may have implications for dose optimization. We developed a novel assay using high-performance liquid chromatography-tandem mass spectrometry (LC-MS/MS) to measure the intracellular concentrations of bedaquiline and its primary metabolite M2 in patients with RR-TB in South Africa. Twenty-one participants were enrolled and underwent sparse sampling of plasma and peripheral blood mononuclear cells (PBMCs) at months 1, 2, and 6 of treatment and at 3 and 6 months after bedaquiline treatment completion. Intensive sampling was performed at month 2. We used noncompartmental analysis to describe plasma and intracellular exposures and a population pharmacokinetic model to explore the relationship between plasma and intracellular pharmacokinetics and the effects of key covariates. Bedaquiline concentrations from month 1 to month 6 of treatment ranged from 94.7 to 2,540 ng/ml in plasma and 16.2 to 5,478 ng/ml in PBMCs, and concentrations of M2 over the 6-month treatment period ranged from 34.3 to 496 ng/ml in plasma and 109.2 to 16,764 ng/ml in PBMCs. Plasma concentrations of bedaquiline were higher than those of M2, but intracellular concentrations of M2 were considerably higher than those of bedaquiline. In the pharmacokinetic modeling, we estimated a linear increase in the intracellular-plasma accumulation ratio for bedaquiline and M2, reaching maximum effect after 2 months of treatment. The typical intracellular-plasma ratios 1 and 2 months after start of treatment were 0.61 (95% confidence interval [CI]: 0.42 to 0.92) and 1.10 (95% CI: 0.74 to 1.63) for bedaquiline and 12.4 (95% CI: 8.8 to 17.8) and 22.2 (95% CI: 15.6 to 32.3) for M2. The intracellular-plasma ratios for both bedaquiline and M2 were decreased by 54% (95% CI: 24 to 72%) in

HIV-positive patients compared to HIV-negative patients. Bedaquiline and M2 were detectable in PBMCs 6 months after treatment discontinuation. M2 accumulated at higher concentrations intracellularly than bedaquiline, supporting in vitro evidence that M2 is the main inducer of phospholipidosis.

DOI: 10.1128/AAC.02399-20
PMID: 34370588

37. **Profiling and identification of novel rpoB mutations in rifampicin-resistant Mycobacterium tuberculosis clinical isolates from Pakistan.**

J Infect Chemother. 2021 Nov;27(11):1578-1583. doi: 10.1016/j.jiac.2021.06.020. Epub 2021 Jul 7.

Qadir M(1), Tahseen S(2), McHugh TD(3), Hussain A(2), Masood F(2), Ahmed N(2), Faryal R(4).

INTRODUCTION: Rifampicin (RIF) is one of the most effective anti-tuberculosis first-line drugs prescribed along with isoniazid. However, the emergence of RIF resistance Mycobacterium tuberculosis (MTB) isolates is a major issue towards tuberculosis (TB) control program in high MDR TB-burdened countries including Pakistan. Molecular data behind phenotypic resistance is essential for better management of RIF resistance which has been linked with mutations in rpoB gene. Since molecular studies on RIF resistance is limited in Pakistan, the current study was aimed to investigate the molecular data of mutations in rpoB gene behind phenotypic RIF resistance isolates in Pakistan.
METHOD: A total of 322 phenotypically RIF-resistant isolates were randomly selected from National TB Reference Laboratory, Pakistan for sequencing while 380 RIF resistance whole-genome sequencing (WGS) of Pakistani isolates (BioProject PRJEB25972), were also analyzed for rpoB mutations.
RESULT: Among the 702 RIF resistance samples, 675 (96.1%) isolates harbored mutations in rpoB in which 663 (94.4%) were detected within the Rifampicin Resistance Determining Region (RRDR) also known as a mutation hot spot region, including three novel. Among these mutations, 657 (97.3%) were substitutions including 603 (89.3%) single nucleotide polymorphism, 49 (7.25%) double and five (0.8%) triple. About 94.4% of Phenotypic RIF resistance strains, exhibited mutations in RRDR, which were also detectable by GeneXpert.
CONCLUSION: Mutations in the RRDR region of rpoB is a major mechanism of RIF resistance in MTB circulating isolates in Pakistan. Molecular detection of drug resistance is a faster and better approach than phenotypic drug susceptibility testing to reduce the time for transmission of RIF resistance strains in population. Such insights will inform the deployment of anti-TB drug regimens and disease control tools and strategies in high burden settings, such as

Pakistan.

DOI: 10.1016/j.jiac.2021.06.020
PMID: 34244055 [Indexed for MEDLINE]

38. **[Factors associated with underreporting of cases of multidrug-resistant tuberculosis in the state of Rio de Janeiro, Brazil: probabilistic database linkage].**

Cad Saude Publica. 2021 Oct 8;37(10):e00293920. doi: 10.1590/0102-311X00293920. eCollection 2021.

Silva MLBD(1)(2), Durovini P(3), Mota P(3), Kritski AL(1).

This study estimated the proportion of underreporting of multidrug-resistant tuberculosis (MDR-TB) and associated factors in the State of Rio de Janeiro, Brazil, as well as the proportion of deaths in this group. A retrospective cohort study was conducted using probabilistic database linkage. Cases with the results of the drug sensitivity test (DST) with MDR-TB pattern recorded in the Laboratory Environment Management System (GAL) from 2010 to 2017 were linked to cases reported to the Special TB Treatments System (SITETB). Simple and multiple logistic regressions were performed to estimate factors associated with underreporting. Death was verified by search for cases in the Mortality Information System (SIM) and in the portal of the Rio de Janeiro State Court of Justice. Of the 651 cases of MDR-TB in the GAL, 165 had not been reported to the SITETB, meaning an underreporting rate of 25.4% in the sample. Among the unreported cases, 61 (37%) were identified in the death records. In the multiple analysis, the fact that the test was ordered by a hospital (OR = 2.86; 95%CI: 1.72-4.73) was associated with underreporting. Overall, the mean turnaround time between ordering the test and releasing the result was 113 days. Among reported cases, the mean time between ordering the test and initiating treatment was 169 days. The results underline the urgent need to strengthen epidemiological surveillance activities for MDR-TB, establish and monitor hospital surveillance centers and routine TB reporting in hospitals, review operational stages, and integrate various information systems to make them more agile and integrated.

DOI: 10.1590/0102-311X00293920
PMID: 34644761

39. **Diverse clinical and social circumstances: developing patient-centred care for DR-TB patients in South Africa.**

Public Health Action. 2021 Sep 21;11(3):120-125. doi: 10.5588/pha.20.0083.

Mitrani L(1), Dickson-Hall L(1), Le Roux S(1), Hill J(2), Loveday M(3)(4), Grant AD(2)(5), Kielmann K(6), Mlisana K(7), Moshabela M(8), Nicol MP(1)(9)(10), Black J(11)(12), Cox H(1)(9).

OBJECTIVE: To describe the medical, socio-economic and geographical profiles of patients with rifampicin-resistant TB (RR-TB) and the implications for the provision of patient-centred care.
SETTING: Thirteen districts across three South African provinces.
DESIGN: This descriptive study examined laboratory and healthcare facility records of 194 patients diagnosed with RR-TB in the third quarter of 2016.
RESULTS: The median age was 35 years; 120/194 (62%) of patients were male. Previous TB treatment was documented in 122/194 (63%) patients and 56/194 (29%) had a record of fluoroquinolone and/or second-line injectable resistance. Of 134 (69%) HIV-positive patients, viral loads were available for 68/134 (51%) (36/68 [53%] had viral loads of >1000 copies/ml) and CD4 counts were available for 92/134 (69%) (20/92 [22%] had CD4 <50 cells/mm3). Patients presented with varying other comorbidities, including hypertension (13/194, 7%) and mental health conditions (11/194, 6%). Of 194 patients, 44 (23%) were reported to be employed. Other socio-economic challenges included substance abuse (17/194, 9%) and ill family members (17/194, 9%). Respectively 13% and 42% of patients were estimated to travel more than 20 km to reach their diagnosing and treatment-initiating healthcare facility.
CONCLUSIONS: RR-TB patients had diverse medical and social challenges highlighting the need for integrated, differentiated and patient-centred healthcare to better address specific needs and underlying vulnerabilities of individual patients.

DOI: 10.5588/pha.20.0083
PMCID: PMC8455019
PMID: 34567987

40. **A systematic review of pharmacoeconomic evaluations on oral diarylquinoline-based treatment for drug-resistant tuberculosis: from high to low burden countries.**

Expert Rev Pharmacoecon Outcomes Res. 2021 Oct;21(5):897-910. doi:

10.1080/14737167.2021.1925111. Epub 2021 Jun 23.

Fekadu G(1), Yao J(1), You JHS(1).

Introduction: There is a rising global interest in the pharmacoeconomic evaluations of bedaquiline (BDQ), a novel oral diarylquinoline, for treatment of drug-resistant tuberculosis (DR-TB).Areas covered: This article systematically reviewed publications retrieved from Medline, American Psychological Association-Psychology information, Web of Science, Embase, Scopus, Science direct, Center for Reviews and Dissemination, and CINAHL Complete during 2010-2020 on pharmacoeconomic studies on BDQ for DR-TB treatment. Ten Markov model-based cost-effectiveness analyses identified were conducted in high (n = 4), intermediate (n = 2), and low (n = 4) TB burden countries.Expert opinion: The paucity of model-based health economic analyses on BDQ-containing regimens for DR-TB indicated that further pharmacoeconomic research of BDQ-based regimens, on the aspects of duration of BDQ treatment, types of DR-TB indicated, and settings of regions and health-systems, is highly warranted to inform global cost-effective use of BDQ-based regimens for DR-TB treatment.

DOI: 10.1080/14737167.2021.1925111
PMID: 33931005 [Indexed for MEDLINE]

41. **Cross-sectional assessment of tuberculosis and HIV prevalence in 13 correctional facilities in Zambia.**

BMJ Open. 2021 Sep 27;11(9):e052221. doi: 10.1136/bmjopen-2021-052221.

Kagujje M(1), Somwe P(2), Hatwiinda S(3), Bwalya J(2), Zgambo T(4), Thornicroft M(3), Bozzani FM(5), Moonga C(3), Muyoyeta M(3).

OBJECTIVE: To determine the prevalence of tuberculosis (TB) and HIV in 13 Zambian correctional facilities.
METHODS: Cross-sectional study.
SETTING: 13 correctional facilities in seven of the 10 provinces in Zambia.
PARTICIPANTS: All incarcerated individuals were eligible for TB and HIV screening and testing. Of the total study population of 9695 individuals, which represent 46.2% of total correctional population at the beginning of the study, 8267 and 8160 were screened for TB and HIV, respectively.
INTERVENTIONS: TB and HIV screening and testing was done between July 2018 and February 2019.
PRIMARY OUTCOME MEASURES: All forms of TB, bacteriologically confirmed TB, drug-resistant TB, HIV.
RESULTS: Prevalence of all forms of TB and bacteriologically confirmed TB was

1599 (1340-1894) per 100 000 population and 1056 (847-1301) per 100 000 population, respectively. Among those with bacteriologically confirmed TB, 4.6% (1.3%-11.4%) had drug-resistant TB.There was no statistically significant difference in the prevalence of all forms of TB, bacteriologically confirmed TB and drug resistant TB between adults and juveniles: (p=0.82), (p=0.23), (p=0.68) respectively. Of the bacteriologically confirmed TB cases, 28.7% were asymptomatic. The prevalence of HIV was 14.3% (13.6%-15.1%). The prevalence of HIV among females was 1.8 times the prevalence of HIV among males (p=0.01). CONCLUSION: Compared with the study in 2011 which screened inmates representing 30% of the country's inmate population, then the prevalence of all forms of TB and HIV in correctional facilities has reduced by about 75% and 37.6%, respectively. However, compared with the general population, the prevalence of all forms of TB and HIV was 3.5 and 1.3 times higher, respectively. TB/HIV programmes in correctional facilities need further strengthening to include aspects of juvenile-specific TB programming and gender responsive HIV programming.

DOI: 10.1136/bmjopen-2021-052221
PMCID: PMC8477336
PMID: 34580101

42. **Preclinical Evaluation of Inhalational Spectinamide-1599 Therapy against Tuberculosis.**

ACS Infect Dis. 2021 Oct 8;7(10):2850-2863. doi: 10.1021/acsinfecdis.1c00213. Epub 2021 Sep 21.

Gonzalez-Juarrero M(1), Lukka PB(2), Wagh S(2), Walz A(1), Arab J(1), Pearce C(1), Ali Z(1), Ryman JT(2), Parmar K(2), Temrikar Z(2), Munoz-Gutierrez J(1), Robertson GT(1), Liu J(3), Lenaerts AJ(1), Daley C(4), Lee RE(3), Braunstein M(5), Hickey AJ(6), Meibohm B(2).

The lengthy treatment time for tuberculosis (TB) is a primary cause for the emergence of multidrug resistant tuberculosis (MDR-TB). One approach to improve TB therapy is to develop an inhalational TB therapy that when administered in combination with oral TB drugs eases and shortens treatment. Spectinamides are new semisynthetic analogues of spectinomycin with excellent activity against Mycobacterium tuberculosis (Mtb), including MDR and XDR Mtb strains. Spectinamide-1599 was chosen as a promising candidate for development of inhalational therapy. Using the murine TB model and intrapulmonary aerosol

delivery of spectinamide-1599, we characterized the pharmacokinetics and efficacy of this therapy in BALB/c and C3HeB/FeJ mice infected with the Mtb Erdman strain. As expected, spectinamide-1599 exhibited dose-dependent exposure in plasma, lungs, and ELF, but exposure ratios between lung and plasma were 12-40 times higher for intrapulmonary compared to intravenous or subcutaneous administration. In chronically infected BALB/c mice, low doses (10 mg/kg) of spectinamide-1599 when administered thrice weekly for two months provide efficacy similar to that of higher doses (50-100 mg/kg) after one month of therapy. In the C3HeB/FeJ TB model, intrapulmonary aerosol delivery of spectinamide-1599 (50 mg/kg) or oral pyrazinamide (150 mg/kg) had limited or no efficacy in monotherapy, but when both drugs were given in combination, a synergistic effect with superior bacterial reduction of >1.8 log10 CFU was observed. Throughout the up to eight-week treatment period, intrapulmonary therapy was well-tolerated without any overt toxicity. Overall, these results strongly support the further development of intrapulmonary spectinamide-1599 as a combination partner for anti-TB therapy.

DOI: 10.1021/acsinfecdis.1c00213
PMID: 34546724

43. **Decreased mortality seen in rifampicin/multidrug-resistant tuberculous meningitis treated with linezolid in Shenzhen, China.**

BMC Infect Dis. 2021 Sep 28;21(1):1015. doi: 10.1186/s12879-021-06705-4.

Fang MT(1), Su YF(1), An HR(2), Zhang PZ(1), Deng GF(1), Liu HM(1), Mao Z(1), Zeng JF(1), Li G(1), Yang QT(3), Wang ZY(4)(5).

BACKGROUND: The morbidity of rifampicin/multidrug-resistant tuberculous meningitis (RR/MDR-TBM) has shown an increasing trend globally. Its mortality rate is significantly higher than that of non-rifampicin/multidrug-resistant tuberculous meningitis (NRR/MDR-TBM). This article aimed to explore risk factors related to RR/MDR-TBM, and compare therapeutic effects of linezolid (LZD)- and non-linezolid-containing regimen for RR/MDR-TB patients in Shenzhen city. Furthermore, we aimed to find a better therapy for pathogen-negative TBM with RR/MDR-TBM related risk factors.
METHODS: We conducted a retrospective study enrolling 137 hospitalized cases with confirmed TBM from June 2014 to March 2020. All patients were divided into RR/MDR-TBM group (12 cases) and NRR/MDR-TBM group (125 cases) based on GeneXpert MTB/RIF and (or) phenotypic drug susceptibility test results using cerebral spinal fluid (CSF). The risk factors related to RR/MDR-TBM were investigated through comparing clinical and examination features between the two groups. The mortality rate of RR/MDR-TBM patients treated with different regimens was

analyzed to compare their respective therapeutic effects. A difference of $P < 0.05$ was considered statistically significant.
RESULTS: Most patients (111/137, 81%) were from southern or southwestern China, and a large proportion (72/137, 52.55%) belonged to migrant workers. 12 cases were RR/MDR-TBM (12/137, 8.8%) while 125 cases were NRR/MDR-TBM (125/137, 91.2%). The proportion of patients having prior TB treatment history in the RR/MDR-TBM group was significantly higher than that of the NRR/MDR-TBM group (6/12 vs. 12/125, 50% vs. 10.5%, $P < 0.01$). No significant difference was observed on other clinical and examination features between the two groups. Mortality was significantly lower in RR/MDR-TBM patients on linezolid-containing treatment regimen than those who were not (0/7 versus 3/5, 0% versus 60%, $P = 0.045$).
CONCLUSIONS: The main related risk factor of RR/MDR-TBM is the history of anti-tuberculosis treatment. Linezolid-containing regimen appears to lower mortality rate of RR/MDR-TBM significantly in our study. We think Linezolid should be evaluated prospectively in the treatment of RR/MDR-TBM.

DOI: 10.1186/s12879-021-06705-4
PMCID: PMC8480033
PMID: 34583653 [Indexed for MEDLINE]

44. **Standardised patient study to assess tuberculosis case detection within the private pharmacy sector in Vietnam.**

BMJ Glob Health. 2021 Oct;6(10):e006475. doi: 10.1136/bmjgh-2021-006475.

Zawahir S(1), Le H(2), Nguyen TA(2), Beardsley J(3), Duc AD(4), Bernays S(5)(6), Viney K(7)(8), Cao Hung T(9), McKinn S(5), Tran HH(4), Nguyen Tu S(10), Velen K(5), Luong Minh T(4), Tran Thi Mai H(4), Nguyen Viet N(11), Nguyen Viet H(2), Nguyen Thi Cam V(2), Nguyen Trung T(2), Jan S(12), Marais BJ(13), Negin J(14), Marks GB(15)(16), Fox G(5).

BACKGROUND: Of the estimated 10 million people affected by (TB) each year, one-third are never diagnosed. Delayed case detection within the private healthcare sector has been identified as a particular problem in some settings, leading to considerable morbidity, mortality and community transmission. Using unannounced standardised patient (SP) visits to the pharmacies, we aimed to evaluate the performance of private pharmacies in the detection and treatment of TB.
METHODS: A cross-sectional study was undertaken at randomly selected private pharmacies within 40 districts of Vietnam. Trained actors implemented two

standardised clinical scenarios of presumptive TB and presumptive multidrug-resistant TB (MDR-TB). Outcomes were the proportion of SPs referred for medical assessment and the proportion inappropriately receiving broad-spectrum antibiotics. Logistic regression evaluated predictors of SPs' referral.
RESULTS: In total, 638 SP encounters were conducted, of which only 155 (24.3%) were referred for medical assessment; 511 (80·1%) were inappropriately offered antibiotics. A higher proportion of SPs were referred without having been given antibiotics if they had presumptive MDR-TB (68/320, 21.3%) versus presumptive TB (17/318, 5.3%; adjusted OR=4.8, 95% CI 2.9 to 7.8). Pharmacies offered antibiotics without a prescription to 89.9% of SPs with presumptive TB and 70.3% with presumptive MDR-TB, with no clear follow-up plan.
CONCLUSIONS: Few SPs with presumptive TB were appropriately referred for medical assessment by private pharmacies. Interventions to improve appropriate TB referral within the private pharmacy sector are urgently required to reduce the number of undiagnosed TB cases in Vietnam and similar high-prevalence settings.

DOI: 10.1136/bmjgh-2021-006475
PMID: 34615661 [Indexed for MEDLINE]

45. **Novel thiomorpholine tethered isatin hydrazones as potential inhibitors of resistant Mycobacterium tuberculosis.**

Bioorg Chem. 2021 Oct;115:105133. doi: 10.1016/j.bioorg.2021.105133. Epub 2021 Jul 3.

Karunanidhi S(1), Chandrasekaran B(1), Karpoormath R(2), Patel HM(3), Kayamba F(1), Merugu SR(1), Kumar V(1), Dhawan S(1), Kushwaha B(1), Mahlalela MC(1).

Novel chemotherapeutic agents against multidrug resistant-tuberculosis (MDR-TB) are urgently needed at this juncture to save the life of TB-infected patients. In this work, we have synthesized and characterized novel isatin hydrazones 4(a-o) and their thiomorpholine tethered analogues 5(a-o). All the synthesized compounds were initially screened for their anti-mycobacterial activity against the H37Rv strain of Mycobacterium tuberculosis (MTB) under level-I testing. Remarkably, five compounds 4f, 4h, 4n, 5f and 5m (IC50 = 1.9 μM to 9.8 μM) were found to be most active, with 4f (IC50 = 1.9 μM) indicating highest inhibition of H37Rv. These compounds were further evaluated at level-II testing against the five drug-resistant strains such as isoniazid-resistant strains (INH-R1 and INH-R2), rifampicin-resistant strains (RIF-R1 and RIF-R2) and

fluoroquinolone-resistant strain (FQ-R1) of MTB. Interestingly, 4f and 5f emerged as the most potent compounds with IC50 of 3.6 μM and 1.9 μM against RIF-R1 MTB strain, followed by INH-R1 MTB strain with IC50 of 3.5 μM and 3.4 μM, respectively. Against FQ-R1 MTB strain, the lead compounds 4f and 5f displayed excellent inhibition at IC50 5.9 μM and 4.9 μM, respectively indicating broad-spectrum of activity. Further, molecular docking, ADME pharmacokinetic and molecular dynamics simulations of the compounds were performed against the DNA gyrase B and obtained encouraging results.

DOI: 10.1016/j.bioorg.2021.105133
PMID: 34329993

46. **Intracellular Accumulation of Novel and Clinically Used TB Drugs Potentiates Intracellular Synergy.**

Microbiol Spectr. 2021 Sep 29:e0043421. doi: 10.1128/Spectrum.00434-21. Online ahead of print.

Tanner L(1), Mashabela GT(2), Omollo CC(2), de Wet TJ(2), Parkinson CJ(3), Warner DF(2)(4), Haynes RK(5), Wiesner L(1).

The therapeutic repertoire for tuberculosis (TB) remains limited despite the existence of many TB drugs that are highly active in in vitro models and possess clinical utility. Underlying the lack of efficacy in vivo is the inability of TB drugs to penetrate microenvironments inhabited by the causative agent, Mycobacterium tuberculosis, including host alveolar macrophages. Here, we determined the ability of the phenoxazine PhX1 previously shown to be active against M. tuberculosis in vitro to differentially penetrate murine compartments, including plasma, epithelial lining fluid, and isolated epithelial lining fluid cells. We also investigated the extent of permeation into uninfected and M. tuberculosis-infected human macrophage-like Tamm-Horsfall protein 1 (THP-1) cells directly and by comparing to results obtained in vitro in synergy assays. Our data indicate that PhX1 (4,750 ± 127.2 ng/ml) penetrates more effectively into THP-1 cells than do the clinically used anti-TB agents, rifampin (3,050 ± 62.9 ng/ml), moxifloxacin (3,374 ± 48.7 ng/ml), bedaquiline (4,410 ± 190.9 ng/ml), and linezolid (770 ± 14.1 ng/ml). Compound efficacy in infected cells correlated with intracellular accumulation, reinforcing the perceived importance of intracellular penetration as a key drug property. Moreover, we detected synergies deriving from redox-stimulatory combinations of PhX1 or clofazimine with the novel prenylated amino-artemisinin WHN296. Finally, we used compound synergies to elucidate the relationship between compound

intracellular accumulation and efficacy, with PhX1/WHN296 synergy levels shown to predict drug efficacy. Collectively, our data support the utility of the applied assays in identifying in vitro active compounds with the potential for clinical development. IMPORTANCE This study addresses the development of novel therapeutic compounds for the eventual treatment of drug-resistant tuberculosis. Tuberculosis continues to progress, with cases of Mycobacterium tuberculosis (M. tuberculosis) resistance to first-line medications increasing. We assess new combinations of drugs with both oxidant and redox properties coupled with a third partner drug, with the focus here being on the potentiation of M. tuberculosis-active combinations of compounds in the intracellular macrophage environment. Thus, we determined the ability of the phenoxazine PhX1, previously shown to be active against M. tuberculosis in vitro, to differentially penetrate murine compartments, including plasma, epithelial lining fluid, and isolated epithelial lining fluid cells. In addition, the extent of permeation into human macrophage-like THP-1 cells and H37Rv-infected THP-1 cells was measured via mass spectrometry and compared to in vitro two-dimensional synergy and subsequent intracellular efficacy. Collectively, our data indicate that development of new drugs will be facilitated using the methods described herein.

DOI: 10.1128/Spectrum.00434-21
PMID: 34585951

47. **Albumin fusion with granulocyte-macrophage colony-stimulating factor acts as an immunotherapy against chronic tuberculosis.**

Cell Mol Immunol. 2021 Oct;18(10):2393-2401. doi: 10.1038/s41423-020-0439-2. Epub 2020 May 7.

Chuang YM(1)(2), He L(1), Pinn ML(3), Tsai YC(1), Cheng MA(1), Farmer E(1), Karakousis PC(3), Hung CF(4).

A long duration of treatment and emerging drug resistance pose significant challenges for global tuberculosis (TB) eradication efforts. Therefore, there is an urgent need to develop novel strategies to shorten TB treatment regimens and to treat drug-resistant TB. Using an albumin-fusion strategy, we created a novel albumin-fused granulocyte-macrophage colony-stimulating factor (albGM-CSF) molecule that harnesses albumin's long half-life and targeting abilities to enhance the biostability of GM-CSF and direct it to the lymph nodes, where the effects of GM-CSF can increase dendritic cell populations crucial for eliciting a potent immune response. In this study, we demonstrate that albGM-CSF serves as a novel immunotherapy for chronic Mycobacterium tuberculosis (Mtb) infections by enhancing GM-CSF biostability in serum. Specifically, albumin is very safe, stable, and has a long half-life, thereby enhancing the biostability of GM-CSF.

In the lungs and draining lymph nodes, albGM-CSF is able to increase the numbers of dendritic cells, which are crucial for the activation of naive T cells and for eliciting potent immune responses. Subcutaneous administration of albGM-CSF alone reduced the mean lung bacillary burden in mice with chronic tuberculosis infection. While GM-CSF administration was associated with IL-1β release from Mtb-infected dendritic cells and macrophages, higher IL-1β levels were observed in albGM-CSF-treated mice with chronic tuberculosis infection than in mice receiving GM-CSF. Albumin fusion with GM-CSF represents a promising strategy for the control of chronic lung tuberculosis infections and serves as a novel therapeutic vaccination platform for other infectious diseases and malignancies.

DOI: 10.1038/s41423-020-0439-2
PMCID: PMC8484439
PMID: 32382128

48. **Discovery of 5-methylpyrimidopyridone analogues as selective antimycobacterial agents.**

Bioorg Med Chem. 2021 Sep 27;49:116426. doi: 10.1016/j.bmc.2021.116426. Online ahead of print.

Wu Y(1), Cheung CY(2), Zhou Y(1), Wang Z(1), Tu Z(1), Cook GM(3), Lu X(4).

With the emergence of multidrug-resistant strains of Mycobacterium tuberculosis (MDR-TB) and extensive drug-resistant strains (XDR-TB), there is an urgent need to develop novel drugs for the treatment of tuberculosis. Here, we designed and synthesized a series of 5-methylpyrimidopyridone analogues as potential antitubercular agents. The most potent compound 6q exhibited a MIC value of 4 μM in vitro against Mycobacterium tuberculosis. The antitubercular activities of the synthesized compounds were impacted by the amantadine and 2-chlorophenyl groups, and were enhanced by the presence of 3-methyl(4-dimethylamino)piperidinylphenyl. Molecular modeling and binding studies suggest that PknB is the potential molecular target of 5-methylpyrimidopyridone compounds. This study provides insights for the future development of new antimycobacterial agents with novel mechanisms of action.

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PMID: 34624820

49. **Predicting the impact of control strategies on the tuberculosis burden in South and North Korea using a mathematical model.**

BMJ Glob Health. 2021 Oct;6(10):e005953. doi: 10.1136/bmjgh-2021-005953.

Cho H(1), Park Y(2), Seok J(1), Yeom JS(3), Choi JY(2), Kim HJ(4), Kang YA(#)(5)(6), Lee J(#)(7).

BACKGROUND: Among high-income countries, South Korea has a considerable tuberculosis (TB) burden; North Korea has one of the highest TB burdens in the world. Predicting the impact of control strategies on the TB burden can help to efficiently implement TB control programmes.
METHODS: We designed a deterministic compartmental model of TB in Korea. After calibration with notification of incidence data from South Korea, the TB burden for 2040 was predicted according to four different intervention strategies: latent TB infection (LTBI) treatment, rapid diagnosis, active case-finding and improvement of the treatment success rate. North Korea's burden in 2040 was similarly estimated by adjusting the model parameters.
RESULTS: In South Korea, the number of patients with drug-susceptible TB (DS-TB) and multidrug-resistant TB (MDR-TB) were predicted to be 27 581 and 625, respectively, in 2025. Active case-finding would lower DS-TB by 6.2% and MDR-TB by 26.7%, respectively, in 2040. The improvement in the success rate of DS-TB treatment would reduce the MDR-TB burden by 34.5%. In North Korea, the number of patients with DS-TB and MDR-TB are, respectively, predicted to be 77 629 and 5409 in 2025. Active case-finding would reduce DS-TB by 22.2% and MDR-TB by 69.7%. LTBI treatment would reduce DS-TB by 20.6% and MDR-TB by 38.6%.
CONCLUSION: The impact of control strategies on the TB burden in South and North Korea was investigated using a mathematical model. The combined intervention strategies would reduce the burden and active case-finding is expected to result in considerable reduction in both South and North Korea.

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PMID: 34620614 [Indexed for MEDLINE]

50. **People Who Inject Drugs and have tuberculosis: Opioid Substitution Therapy improves treatment outcomes in Ukraine.**

J Infect Dev Ctries. 2021 Sep 29;15(9.1):51S-57S. doi: 10.3855/jidc.13759.

Fomenko T(1), Meteliuk A(2), Korinchuk L(3), Denisiuk O(2), Aslanyan G(4), Islam Z(2), Zachariah R(4).

INTRODUCTION: Opioid substitution therapy (OST) is one of the pillars of harm reduction strategies for People Who Inject Drugs (PWID). It should be an integral part of tuberculosis (TB) care to increase the uptake, compliance and effectiveness of treatment and also curtail risk behaviors. We aimed to compare TB treatment outcomes in relation to OST among PWID in six regions of Ukraine. METHODOLOGY: A retrospective cohort study using routine programmatic data from centers offering integrated TB and OST (December 2016 - May 2020). OST involved use of methadone or buprenorphine. TB treatment outcomes were standardized. RESULTS: Of 228 PWID (85% male) diagnosed with TB, 104 (46%) had drug-sensitive and 124 (64%) drug-resistant TB. The majority had pulmonary TB (95%), 64 (28%) were HCV-positive and 179 (78%) were HIV-positive, 91% of the latter were also on antiretroviral therapy. There were 114 (50%) PWID with TB on OST. For drug-sensitive TB (n=104), treatment success was significantly higher (61%) in those on adjunctive OST than those not on OST (42%, P<0.001). Similarly, for drug-resistant TB (n=124) treatment success was also significantly higher when individuals were on OST (43%) compared to when not on OST (26%, P<0.001). CONCLUSIONS: This operational research study shows that OST is associated with significantly improved treatment success in PWID and can contribute to achieving Universal Health Coverage and the WHO Flagship Initiative "Find.Treat.All. #End TB". We advocate for the scale-up of this intervention in Ukraine.

DOI: 10.3855/jidc.13759
PMID: 34609960

51. **Effectiveness of GenoType MTBDRsl in excluding TB drug resistance in a clinical trial.**

Int J Tuberc Lung Dis. 2021 Oct 1;25(10):839-845. doi: 10.5588/ijtld.21.0212.

Ejo M(1), Van Deun A(2), Nunn A(3), Meredith S(3), Ahmed S(3), Dalai D(4), Tumenbayar O(4), Tsogt B(5), Dat PT(6), Ha DTM(6), Hang PT(6), Kokebu D(7), Teferi M(8), Mebrahtu T(8), Ngubane N(9), Moodliar R(10), Duckworth L(10), Conradie F(11), Enduwamahoro E(12), Keysers J(12), De Rijk P(12), Mulders W(12), Diro E(13), Rigouts L(14), de Jong BC(12), Torrea G(12).

OBJECTIVES: To assess the performance of the GenoType MTBDRsl v1, a line-probe assay (LPA), to exclude baseline resistance to fluoroquinolones (FQs) and

second-line injectables (SLIs) in the Standard Treatment Regimen of Anti-tuberculosis Drugs for Patients With MDR-TB 1 (STREAM 1) trial.METHODS: Direct sputum MTBDRsl results in the site laboratories were compared to indirect phenotypic drug susceptibility testing (pDST) results in the central laboratory, with DNA sequencing as a reference standard.RESULTS: Of 413 multidrug-resistant TB (MDR-TB) patients tested using MTBDRsl and pDST, 389 (94.2%) were FQ-susceptible and 7 (1.7%) FQ-resistant, while 17 (4.1%) had an inconclusive MTBDRsl result. For SLI, 372 (90.1%) were susceptible, 5 (1.2%) resistant and 36 (8.7%) inconclusive. There were 9 (2.3%) FQ discordant pDST/MTBDRsl results, of which 3 revealed a mutation and 5 (1.3%) SLI discordant pDST/MTBDRsl results, none of which were mutants on sequencing. Among the 17 FQ- and SLI MTBDRsl-inconclusive samples, sequencing showed 1 FQ- and zero SLI-resistant results, similar to frequencies among the conclusive MTBDRsl. The majority of inconclusive MTBDRsl results were associated with low bacillary load samples (acid-fast bacilli smear-negative or scantily positive) compared to conclusive results ($P < 0.001$).CONCLUSION: MTBDRsl can facilitate the rapid exclusion of FQ and SLI resistances for enrolment in clinical trials.

DOI: 10.5588/ijtld.21.0212
PMID: 34615581

52. **Baseline assessment of pharmacovigilance activities in four sub-Saharan African countries: a perspective on tuberculosis.**

BMC Health Serv Res. 2021 Oct 8;21(1):1062. doi: 10.1186/s12913-021-07043-6.

Tiemersma EW(1), Ali I(2), Alemu A(3), Avong YK(4)(5), Duga A(6)(7), Elagbaje C(8), Isah A(9), Kay A(10)(11), Mmbaga BT(12)(13), Mmari E(14), Mwamwitwa K(15), Nhlabatsi S(7), Sintayehu K(16), Arefayne A(16), Teferi M(17), Cobelens F(18), Härmark L(19).

BACKGROUND: New medicines have become available for the treatment of drug-resistant tuberculosis (DR-TB) and are introduced in sub-Saharan Africa (SSA) by the national TB programs (NTPs) through special access schemes. Pharmacovigilance is typically the task of national medicines regulatory agencies (NMRAs), but the active drug safety monitoring and management (aDSM) recommended for the new TB medicines and regimens was introduced through the NTPs. We assessed the strengths and challenges of pharmacovigilance systems in Eswatini, Ethiopia, Nigeria and Tanzania, focusing on their capacity to monitor safety of medicines registered and not registered by the NMRAs for the treatment of DR-TB.
METHODS: Assessment visits were conducted to all four countries by a multidisciplinary team. We used a pharmacovigilance indicator tool derived from

existing tools, interviewed key stakeholders, and visited health facilities where DR-TB patients were treated with new medicines. Assessment results were verified with the local NMRAs and NTPs.
RESULTS: Most countries have enabling laws, regulations and guidelines for the conduct of pharmacovigilance by the NMRAs. The relative success of NTP-NMRA collaboration is much influenced by interpersonal relationships between staff. Division of roles and responsibilities is not always clear and leads to duplication and unfulfilled tasks (e.g. causality assessment). The introduction of aDSM has increased awareness among DR-TB healthcare providers.
CONCLUSION: aDSM has created awareness about the importance of pharmacovigilance among NTPs. In the future, a push for conducting pharmacovigilance through public health programs seems useful, but this needs to coincide with increased collaboration with between public health programs and NMRAs with clear formulation of roles and responsibilities.

DOI: 10.1186/s12913-021-07043-6
PMCID: PMC8499544
PMID: 34625085 [Indexed for MEDLINE]

53. **Mycobacterium tuberculosis strain lineage in mixed tribal population across India and Andaman Nicobar Island.**

World J Microbiol Biotechnol. 2021 Oct 12;37(11):192. doi: 10.1007/s11274-021-03164-6.

Dusthackeer A(#)(1), Kumar A(#)(2), Mohanvel SK(#)(3), Mahizhaveni B(2), Shivakumar S(2), Raghavi S(4), Azhagendran S(4), Vetrivel S(4), Rao VG(5), Yadav R(5), Paluru V(6), Purthy AJ(7), Hussain T(8), Kashyap V(9), Devi KR(10), Krishnan AKI(11), Anand P(12), Das P(13), Bansal AK(14), Das M(15), Kaur H(15), Raghunath D(16), Mondal R(17), Thomas BE(4).

In India, the tribal population constitutes almost 8.6% of the nation's total population. Despite their large presence, there are only a few reports available on Mycobacterium tuberculosis (M. tb) strain prevalence in Indian tribal communities considering the mobile nature of this population and also the influence of the mainstream populations they coexist within many areas for their livelihood. This study attempts to provide critical information pertaining to the TB strain diversity, its public health implications, and distribution among the tribal population in eleven Indian states and Andaman & Nicobar (A&N) Island. The study employed a population-based molecular approach. Clinical isolates were received from 66 villages (10 states and Island) and these

villages were selected by implying situation analysis. A total of 78 M. tb clinical isolates were received from 10 different states and A&N Island. Among these, 16 different strains were observed by spoligotyping technique. The major M. tb strains spoligotype belong to the Beijing, CAS1_DELHI, and EAI5 family of M. tb strains followed by EAI1_SOM, EAI6_BGD1, LAM3, LAM6, LAM9, T1, T2, U strains. Drug-susceptibility testing (DST) results showed almost 15.4% of clinical isolates found to be resistant to isoniazid (INH) or rifampicin (RMP) + INH. Predominant multidrug-resistant (MDR-TB) isolates seem to be Beijing strain. Beijing, CAS1_DELHI, EAI3_IND, and EAI5 were the principal strains infecting mixed tribal populations across India. Despite the small sample size, this study has demonstrated higher diversity among the TB strains with significant MDR-TB findings. Prevalence of Beijing MDR-TB strains in Central, Southern, Eastern India and A&N Island indicates the transmission of the TB strains.

DOI: 10.1007/s11274-021-03164-6
PMID: 34637049

54. **Genetic diversity of candidate loci linked to Mycobacterium tuberculosis resistance to bedaquiline, delamanid and pretomanid.**

Sci Rep. 2021 Sep 30;11(1):19431. doi: 10.1038/s41598-021-98862-4.

Gómez-González PJ(1), Perdigao J(2), Gomes P(2), Puyen ZM(3), Santos-Lazaro D(3), Napier G(1), Hibberd ML(1), Viveiros M(4), Portugal I(2), Campino S(1), Phelan JE(1), Clark TG(5)(6)(7).

Tuberculosis (TB), caused by Mycobacterium tuberculosis, is one of the deadliest infectious diseases worldwide. Multidrug and extensively drug-resistant strains are making disease control difficult, and exhausting treatment options. New anti-TB drugs bedaquiline (BDQ), delamanid (DLM) and pretomanid (PTM) have been approved for the treatment of multi-drug resistant TB, but there is increasing resistance to them. Nine genetic loci strongly linked to resistance have been identified (mmpR5, atpE, and pepQ for BDQ; ddn, fgd1, fbiA, fbiB, fbiC, and fbiD for DLM/PTM). Here we investigated the genetic diversity of these loci across >33,000 M. tuberculosis isolates. In addition, epistatic mutations in mmpL5-mmpS5 as well as variants in ndh, implicated for DLM/PTM resistance in M. smegmatis, were explored. Our analysis revealed 1,227 variants across the nine genes, with the majority (78%) present in isolates collected prior to the roll-out of BDQ and DLM/PTM. We identified phylogenetically-related mutations, which are unlikely to be resistance associated, but also high-impact variants

such as frameshifts (e.g. in mmpR5, ddn) with likely functional effects, as well as non-synonymous mutations predominantly in MDR-/XDR-TB strains with predicted protein destabilising effects. Overall, our work provides a comprehensive mutational catalogue for BDQ and DLM/PTM associated genes, which will assist with establishing associations with phenotypic resistance; thereby, improving the understanding of the causative mechanisms of resistance for these drugs, leading to better treatment outcomes.

DOI: 10.1038/s41598-021-98862-4
PMCID: PMC8484543
PMID: 34593898

55. **FAST tuberculosis transmission control strategy speeds the start of tuberculosis treatment at a general hospital in Lima, Peru.**

Infect Control Hosp Epidemiol. 2021 Oct 6:1-7. doi: 10.1017/ice.2021.422. Online ahead of print.

Tierney DB(1)(2), Orvis E(3), Nathavitharana RR(2)(4), Hurwitz S(1)(2), Tintaya K(5), Vargas D(6), Segura P(6), de la Gala S(5), Lecca L(5), Mitnick CD(#)(1)(7), Nardell EA(#)(1)(2).

OBJECTIVE: To evaluate the effect of the FAST (Find cases Actively, Separate safely, Treat effectively) strategy on time to tuberculosis diagnosis and treatment for patients at a general hospital in a tuberculosis-endemic setting.
DESIGN: Prospective cohort study with historical controls.
PARTICIPANTS: Patients diagnosed with pulmonary tuberculosis during hospitalization at Hospital Nacional Hipolito Unanue in Lima, Peru.
METHODS: The FAST strategy was implemented from July 24, 2016, to December 31, 2019. We compared the proportion of patients with drug susceptibility testing and tuberculosis treatment during FAST to the 6-month period prior to FAST. Times to diagnosis and tuberculosis treatment were also compared using Kaplan-Meier plots and Cox regressions.
RESULTS: We analyzed 75 patients diagnosed with pulmonary tuberculosis through FAST. The historical cohort comprised 76 patients. More FAST patients underwent drug susceptibility testing (98.7% vs 57.8%; OR, 53.8; P < .001), which led to the diagnosis of drug-resistant tuberculosis in 18 (24.3%) of 74 of the prospective cohort and 4 (9%) of 44 of the historical cohort (OR, 3.2; P = .03). Overall, 55 FAST patients (73.3%) started tuberculosis treatment during hospitalization compared to 39 (51.3%) controls (OR, 2.44; P = .012). FAST reduced the time from hospital admission to the start of TB treatment (HR, 2.11;

95% CI, 1.39-3.21; P < .001).
CONCLUSIONS: Using the FAST strategy improved the diagnosis of drug-resistant tuberculosis and the likelihood and speed of starting treatment among patients with pulmonary tuberculosis at a general hospital in a tuberculosis-endemic setting. In these settings, the FAST strategy should be considered to reduce tuberculosis transmission while simultaneously improving the quality of care.

DOI: 10.1017/ice.2021.422
PMID: 34612182

56. **Computational identification and characterization of antigenic properties of Rv3899c of Mycobacterium tuberculosis and its interaction with human leukocyte antigen (HLA).**

Immunogenetics. 2021 Oct;73(5):357-368. doi: 10.1007/s00251-021-01220-x. Epub 2021 Jul 6.

Das R(1), Eniyan K(2)(3), Bajpai U(4).

A rise in drug-resistant tuberculosis (TB) cases demands continued efforts towards the discovery and development of drugs and vaccines. Secretory proteins of Mycobacterium tuberculosis (H37Rv) are frequently studied for their antigenicity and their scope as protein subunit vaccines requires further analysis. In this study, Rv3899c of H37Rv emerges as a potential vaccine candidate on its evaluation by several bioinformatics tools. It is a non-toxic, secretory protein with an 'immunoglobulin-like' fold which does not show similarity with a human protein. Through BlastP and MEME suite analysis, we found Rv3899c homologs in several mycobacterial species and its antigenic score (0.54) to compare well with the known immunogens such as ESAT-6 (0.56) and Rv1860 (0.52). Structural examination of Rv3899c predicted ten antigenic peptides, an accessibility profile of the antigenic determinants constituting B cell epitope-rich regions and a low abundance of antigenic regions (AAR) value. Significantly, STRING analysis showed ESX-2 secretion system proteins and antigenic PE/PPE proteins of H37Rv as the interacting partners of Rv3899c. Further, molecular docking predicted Rv3899c to interact with human leukocyte antigen HLA-DRB1*04:01 through its antigenically conserved motif (RAAEQQRLQRIVDAVARQEPRISWAAGLRDDGTT). Interestingly, the binding affinity was observed to increase on citrullination of its Arg1 residue. Taken together, the computational characterization and predictive information suggest Rv3899c to be a promising TB vaccine candidate, which should be validated experimentally.

DOI: 10.1007/s00251-021-01220-x
PMID: 34228167 [Indexed for MEDLINE]

57. **9-12 months short treatment for patients with MDR-TB increases treatment success in Kyrgyzstan.**

J Infect Dev Ctries. 2021 Sep 29;15(9.1):66S-74S. doi: 10.3855/jidc.13757.

Zhdanova E(1), Goncharova O(2), Davtyan H(3), Alaverdyan S(3), Sargsyan A(3), Harries AD(4), Maykanaev B(2).

INTRODUCTION: MDR/RR-TB is a growing problem in Kyrgyzstan. In 2005, the country introduced standard or individualized treatment for 20-24 months. Because of poor treatment outcomes, in 2017 a short treatment with strict eligibility criteria was introduced. The aim of this study was to compare characteristics and treatment outcomes of MDR/RR-TB patients receiving short (9-12 months) treatment in 2017 with those receiving standard or individualized (20-24 months) treatment in 2016/2017.
METHODOLOGY: A comparative cohort study using routine programmatic data. Characteristics, sputum culture conversion and treatment outcomes were compared between those on short treatment with those on standard/individualized treatment using the chi-square test, crude and adjusted risk ratios (RR and aRR).
RESULTS: The study included 274, 82 and 132 patients on standard, individualized and short treatment, respectively. There were more females, fewer migrants/homeless and unemployed and more new TB patients on short treatment compared with the other two groups. A favorable outcome (cure and treatment completed) was significantly higher in short treatment patients (83%) compared with those on standard (50%) or individualized (59%) treatment ($p < 0.001$). There was higher 1-month sputum culture conversion with short treatment (35%) compared with the other two groups (19% and 24%, $p < 0.05$). Short treatment (aRR 1.6, 1.4-1.8), female gender (aRR 1.2, 1.1-1.4), not being homeless (aRR 12.9, 4.5-17.3) and having new TB (aRR 1.3, 1.0-1.5) were independently associated with a favorable outcome.
CONCLUSIONS: The treatment success was higher in selected MDR-TB patients given short treatment in Kyrgyzstan: this regimen should be scaled-up to all MDR-TB patients.

DOI: 10.3855/jidc.13757
PMID: 34609962

58. **Separation and Characterization of Novel Degradation and Process Related Impurities of Bedaquiline Bulk Drug.**

J Chromatogr Sci. 2021 Oct 5:bmab117. doi: 10.1093/chromsci/bmab117. Online ahead of print.

Vanavi PJ(1), Rajput SJ(1).

Bedaquiline (BDQ) is a new drug approved by United States Food and Drug Administration (USFDA) in 2012 for the treatment of drug-resistant tuberculosis, which has become a major threat globally. The manuscript presents the development of three liquid chromatography (LC) based analytical methods. The first is a stability indicating RP-HPLC (reverse phase-high performance liquid chromatography) method to analyze the BDQ in presence of its degradation products. Another UPLC/ESI-MS (ultra-performance liquid chromatography/electron spray ionization-mass spectrometry) method was developed for the identification of different degradation based and process related impurities and the third, preparative HPLC method was developed for the isolation of major degradation products. Eleven degradation products and one process related impurity were identified using UPLC/ESI-MS whereas preparative HPLC was used to isolate two degradation products and their chemical structure was elucidated using nuclear magnetic resonance, mass and infra-red spectral data.

DOI: 10.1093/chromsci/bmab117
PMID: 34607340

59. **Engaging with the private healthcare sector for the control of tuberculosis in India: cost and cost-effectiveness.**

BMJ Glob Health. 2021 Oct;6(10):e006114. doi: 10.1136/bmjgh-2021-006114.

Arinaminpathy N(1), Nandi A(2)(3), Vijayan S(4), Jha N(5), Nair SA(6), Kumta S(7), Dewan P(8), Rade K(9), Vadera B(10), Rao R(11), Sachdeva KS(12).

BACKGROUND: The control of tuberculosis (TB) in India is complicated by the presence of a large, disorganised private sector where most patients first seek care. Following pilots in Mumbai and Patna (two major cities in India), an initiative known as the 'Public-Private Interface Agency' (PPIA) is now being

expanded across the country. We aimed to estimate the cost-effectiveness of scaling up PPIA operations, in line with India's National Strategic Plan for TB control.
METHODS: Focusing on Mumbai and Patna, we collected cost data from implementing organisations in both cities and combined this data with models of TB transmission dynamics. Estimating the cost per disability adjusted life years (DALY) averted between 2014 (the start of PPIA scale-up) and 2025, we assessed cost-effectiveness using two willingness-to-pay approaches: a WHO-CHOICE threshold based on per-capita economic productivity, and a more stringent threshold incorporating opportunity costs in the health system.
FINDINGS: A PPIA scaled up to ultimately reach 50% of privately treated TB patients in Mumbai and Patna would cost, respectively, US$228 (95% uncertainty interval (UI): 159 to 320) per DALY averted and US$564 (95% uncertainty interval (UI): 409 to 775) per DALY averted. In Mumbai, the PPIA would be cost-effective relative to all thresholds considered. In Patna, if focusing on adherence support, rather than on improved diagnosis, the PPIA would be cost-effective relative to all thresholds considered. These differences between sites arise from variations in the burden of drug resistance: among the services of a PPIA, improved diagnosis (including rapid tests with genotypic drug sensitivity testing) has greatest value in settings such as Mumbai, with a high burden of drug-resistant TB.
CONCLUSIONS: To accelerate decline in TB incidence, it is critical first to engage effectively with the private sector in India. Mechanisms such as the PPIA offer cost-effective ways of doing so, particularly when tailored to local settings.

DOI: 10.1136/bmjgh-2021-006114
PMCID: PMC8493898
PMID: 34610905 [Indexed for MEDLINE]

60. **Does optimized adherence support improve treatment outcomes in RR / MDR-TB patients on 18-20 months regimen in Tbilisi, Georgia?**

J Infect Dev Ctries. 2021 Sep 29;15(9.1):34S-42S. doi: 10.3855/jidc.13783.

Jomidava T(1), Khogali M(2), Sereda Y(3), Avaliani Z(4), Davitashvili M(4), Madzgharashvili M(4), Tukvadze N(4), Chaphurishvili L(4), Chincharauli M(4), Kipiani M(4).

INTRODUCTION: Adherence to second-line antituberculosis drug is challenging. A

combination of strategies needs to be implemented to achieve adherence. In Georgia an optimized adherence support (OAS) - a package of education, psychosocial support and adherence counselling - was added to the already existing package of adherence support (supervised treatment, adherence incentives, transport cost reimbursement) to improve adherence and increase treatment success. We assessed the additive benefits of OAS on adherence and treatment outcomes.
METHODOLOGY: This was a before and after cohort study using routine programme data in the National Center for Tuberculosis and Lung Diseases in Tbilisi. All adult rifampicin- and multidrug-resistant tuberculosis (RR/MDR-TB) patients enrolled for treatment under directly observed therapy in the NCTLD during the period before (June 2015 - January 2016) and after (June 2017 - January 2018) were included in the study. Primary outcomes were: i) adequate adherence defined as ≥ 85% of days covered by TB medication during the whole treatment period; ii) final treatment outcomes.
RESULTS: Of 221 RR/MDR-TB, most patients were male (76%, N = 167) with a mean age of 41 ± 14 years. Adherence data was available for 111 patients in the 'before' and 97 patients in the 'after' cohort. Adequate adherence was achieved by 62% (69/111) in the 'before' and 70% (68/97) in the 'after' cohort (p = 0.290). Overall treatment success was 64% (73/114) and 63% (67/107) in the 'before' and 'after' cohorts respectively (p = 0.937).
CONCLUSIONS: Implementation of OAS had modest effect on adherence and had no additive benefits on treatment outcomes among RR/MDR-TB patients on 18-20 months regimen.

DOI: 10.3855/jidc.13783
PMID: 34609958

61. **The Magnitude of MTB and Rifampicin Resistance MTB Using Xpert-MTB/RIF Assay Among Tuberculosis Suspected Patients in Gedeo Zone, Southern Ethiopia.**

Infect Drug Resist. 2021 Sep 24;14:3961-3969. doi: 10.2147/IDR.S327607. eCollection 2021.

Diriba K(1), Awulachew E(1), Churiso G(2).

BACKGROUND: Tuberculosis (TB) remains a major global health problem causing death among millions of people each year. The new barrier that challenges the control of tuberculosis is the emerging and the increasing number of

drug-resistant TB that becomes a world concern. This study aimed to determine the magnitude of rifampicin-resistant Mycobacterium tuberculosis (RR-MTB) among presumptive TB patients attending Dilla University Referral Hospital, Gedeo Zone, Ethiopia.
METHODS: A retrospective cross-sectional study was conducted at Dilla University Referral Hospital from January 2014 to December 2020. Sputum results were done using Xpert MTB/RIF assay and other necessary data were collected from the registration logbooks using a standardized data extraction format and analyzed using SPSS version 23 statistical software.
RESULTS: A total of 17,745 presumptive TB patients were included, of which 62.2% were males. The overall prevalence of Mycobacterium tuberculosis (MTB) was 11.8%, of which 5.1% were confirmed to have RR-MTB. Extra-pulmonary TB was reported in 1.5% of the study participants. The highest prevalence of MTB and RR-MTB was recorded in 2017 with a prevalence of 20.1% and 8.5%, respectively. All age groups were significantly associated with a higher prevalence of MTB ($p < 0.036$). TB patients with a history of previous treatment and HIV positive were significantly associated with MTB ($P < 0.021$), while RR-MTB was only significantly associated with patients with a history of previous treatment ($P < 0.018$).
CONCLUSION: A high magnitude of MTB and RR-MTB was reported among TB patients with HIV and a history of previous treatment. Therefore, coordinated efforts should be applied to the improvement of treatment adherence of known TB cases, and appropriate control and prevention methods to reduce the emergence and increase of MTB and RR-MTB cases.

DOI: 10.2147/IDR.S327607
PMCID: PMC8478339
PMID: 34594119

62. **Treatment Outcomes of Patients with Multidrug-Resistant Tuberculosis: Concern to Bedaquiline.**

Tuberc Respir Dis (Seoul). 2021 Oct;84(4):338-339. doi: 10.4046/trd.2021.0115. Epub 2021 Aug 3.

Putra ON(1), Hidayatullah AYN(1).

DOI: 10.4046/trd.2021.0115
PMCID: PMC8497772
PMID: 34343423

63. **Breaking the paradigm: Optimized Case Finding multiplies tuberculosis detection among key populations in Ukraine.**

J Infect Dev Ctries. 2021 Sep 29;15(9.1):75S-81S. doi: 10.3855/jidc.13806.

Masiuk L(1), Denisiuk O(1), Geliukh E(1), Aslanyan G(2), Zachariah R(2), Islam Z(1).

INTRODUCTION: In 2018, there were 3 million "missed" tuberculosis (TB) cases globally, much of which was disproportionally concentrated among key populations. To enhance TB case-finding, an Optimized Case Finding (OCF) strategy involving all contacts within the social network of an index TB case was introduced in five regions of Ukraine. We assessed TB detection and linkage to TB treatment using OCF in key populations.
METHODOLOGY: A cohort study using routine program data (July 2018 - March 2020). OCF empowers the index TB case to identify and refer up to eight close contacts within his/her social network for TB investigations.
RESULTS: Of 726 index TB cases in key populations, 6,998 close contacts were referred for TB investigations and 275 were diagnosed with TB (183 drug-sensitive and 92 drug-resistant TB). The TB case detection rate was 3,930/100,000 and the Numbers Needed to Investigate to detect one TB case was 25. TB was most frequent among people who inject drugs and homeless groups. Compared to TB detection using routine household case finding within the general population (1,090/100,000), OCF was 3.6-fold more effective and when compared to passive case finding in the general population (60/100,000), OCF was 66 times more effective. 99% (273) of TB patients were linked to care and initiated TB treatment.
CONCLUSIONS: The OCF strategy among key populations is very effective in identifying TB cases and involving them for treatment through the recruitment of the contacts from the risk social networks. We advocate to scale-up this case finding strategy in Ukraine and beyond.

DOI: 10.3855/jidc.13806
PMID: 34633786

64. **The Mur Enzymes Chink in the Armour of Mycobacterium tuberculosis cell wall.**

Eur J Med Chem. 2021 Oct 15;222:113568. doi: 10.1016/j.ejmech.2021.113568. Epub 2021 Jun 2.

Shinde Y(1), Ahmad I(1), Surana S(1), Patel H(2).

TUBERCULOSIS: (TB) transmitted by Mycobacterium tuberculosis (Mtb) is one of the top 10 causes of death globally. Currently, the widespread occurrence of resistance toward Mtb strains is becoming a significant concern to public health. This scenario exaggerated the need for the discovery of novel targets and their inhibitors. Targeting the "Mtb cell wall peptidoglycan synthesis" is an attractive strategy to overcome drug resistance. Mur enzymes (MurA-MurF) play essential roles in the peptidoglycan synthesis by catalyzing the ligation of key amino acid residues to the stem peptide. These enzymes are unique and confined to the eubacteria and are absent in humans, representing potential targets for anti-tubercular drug discovery. Mtb Mur ligases with the same catalytic mechanism share conserved amino acid regions and structural features that can conceivably exploit for the designing of the inhibitors, which can simultaneously target more than one isoforms (MurC-MurF) of the enzyme. In light of these findings in the current review, we have discussed the recent advances in medicinal chemistry of Mtb Mur enzymes (MurA-MurF) and their inhibitors, offering attractive multi-targeted strategies to combat the problem of drug-resistant in M. tuberculosis.

DOI: 10.1016/j.ejmech.2021.113568
PMID: 34118719 [Indexed for MEDLINE]

65. **Design and synthesis of 2-(2-isonicotinoylhydrazineylidene)propanamides as InhA inhibitors with high antitubercular activity.**

Eur J Med Chem. 2021 Nov 5;223:113668. doi: 10.1016/j.ejmech.2021.113668. Epub 2021 Jun 23.

Pflégr V(1), Horváth L(2), Stolaříková J(3), Pál A(4), Korduláková J(4), Bősze S(2), Vinšová J(1), Krátký M(5).

Based on successful antitubercular isoniazid scaffold we have designed its "mee-too" analogues by a combination of this drug linked with substituted anilines through pyruvic acid as a bridge. Lipophilicity important for passive diffusion through impenetrable mycobacterial cell wall was increased by halogen substitution on the aniline. We prepared twenty new 2-(2-isonicotinoylhydrazineylidene)propanamides that were assayed against susceptible Mycobacterium tuberculosis H37Rv, nontuberculous mycobacteria, and also multidrug-resistant tuberculous strains (MDR-TB). All the compounds showed excellent activity not only against Mtb. (minimum inhibitory concentrations,

MIC, from ≤0.03 μM), but also against M. kansasii (MIC ≥2 μM). The most active molecules have CF3 and OCF3 substituent in the position 4 on the aniline ring. MIC against MDR-TB were from 8 μM. The most effective derivatives were used for the mechanism of action investigation. The treatment of Mtb. H37Ra with tested compounds led to decreased production of mycolic acids and the strains overproducing InhA were more resistant to them. These results confirm that studied compounds inhibit the enoyl-acyl carrier protein reductase (InhA) in mycobacteria. The compounds did not show any cytotoxic and cytostatic activity for HepG2 cells. The amides can be considered as a promising scaffold for antitubercular drug discovery having better antimicrobial properties than original isoniazid together with a significantly improved pharmaco-toxicological profile.

DOI: 10.1016/j.ejmech.2021.113668
PMID: 34198149 [Indexed for MEDLINE]

66. **Effect of food insecurity on mental health of patients with tuberculosis in Southwest Ethiopia: a prospective cohort study.**

BMJ Open. 2021 Sep 28;11(9):e045434. doi: 10.1136/bmjopen-2020-045434.

Soboka M(1)(2), Tesfaye M(3)(4), Adorjan K(3)(5)(6), Krahl W(3)(7), Tesfaye E(2), Yitayih Y(2), Strobl R(8)(9), Grill E(3)(8)(9).

OBJECTIVE: The objective of this study is to investigate the effect of food insecurity on the mental health of patients with tuberculosis (TB) in Ethiopia.
DESIGN: A prospective cohort study.
SETTING: Health centres and hospitals located in Jimma zone, Southwest Ethiopia.
PARTICIPANTS: Patients with TB who had recently been diagnosed with TB and started directly observed treatment in the selected 26 health institutions from October 2017 to October 2018. A total of 268 patients were followed for 6 months and data were collected at recruitment and two follow-up visits (at 2 and 6 months). Patients with multidrug-resistant TB were not included in the study.
MAIN OUTCOME MEASURES: Mental distress was measured by the Self-Reporting Questionnaire-20 while food insecurity was assessed by using the Household Food Insecurity Access Scale.
RESULTS: A total of 268 patients were recruited and there was no lost to follow-up. The prevalence of food insecurity at baseline, first and second follow-up was 49.3%, 45.9% and 39.6%, respectively. Of these, 28.0% of them reported severe food insecurity at baseline which declined to 23.5% at the end of the sixth month. Likewise, the prevalence of mental distress at baseline was

61.2% but declined to 22.0% at the second follow-up. At baseline, 77.3% of patients with mental distress reported severe food insecurity but declined to 46.0% at second follow-up. In the final model, severe food insecurity (OR 4.7, 95% CI 2.4 to 9.4) and being a government employee (adjusted odds ratio (aOR) 0.3, 95% CI 0.1 to 0.9) were associated with mental distress.
CONCLUSION: In this study, food insecurity was associated with mental distress over the course of follow-up. Likewise, there is a high prevalence of food insecurity and mental distress among patients with TB on treatment. Therefore, early assessment and interventions for food insecurity may improve the mental health of patients with TB on treatment.

DOI: 10.1136/bmjopen-2020-045434
PMCID: PMC8479992
PMID: 34588229

67. **Recurrent pulmonary tuberculosis after treatment success: a population-based retrospective study in China.**

Clin Microbiol Infect. 2021 Sep 30:S1198-743X(21)00546-2. doi: 10.1016/j.cmi.2021.09.022. Online ahead of print.

Ruan QL(1), Yang QL(1), Sun F(1), Liu W(2), Shen YJ(1), Wu J(1), Jiang N(3), Zhou JY(1), Shao LY(4), Zhang WH(5).

OBJECTIVES: Post-treatment recurrence remains a challenge for the global control of tuberculosis (TB). This study investigated longitudinal data on pulmonary TB recurrence rates and its risk factors among successfully treated smear-positive tuberculosis cases in China.
METHODS: From 1 January 2009 to 31 December 2016, we evaluated 33,441 treatment-naïve patients diagnosed with sputum smear-positive, non-multidrug-resistant TB in Hangzhou, China. We included the data of 9,828 patients with TB who were successfully treated.
RESULTS: A total of 4.9% were recurrent cases (479/9,828), identified within a median observation period lasting 1,565 days. Altogether, 51.1% (245/479) of the recurrences occurred within one year. The cumulative 2- and 5-year recurrence rates were 3.90% (95% confidence interval [CI], 3.3%-4.5%) and 5.4% (95% CI, 4.8%-6.0%), respectively. Prolonged treatment (over 7 months) was occurred in 64.7% (6,363/9,828), with median treatment duration of 242 (interquartile range, 195-348) days. Male sex (adjusted hazard ratio [aHR] [95% CI] = 1.61 [1.30-2.00], P<0.001), ≥ 60-years age (aHR [95% CI] = 2.03 [1.70-2.44],

P<0.001), pulmonary cavity (aHR [95% CI] = 1.51 [1.25-1.82], P<0.001) and sputum positive at 2 months (aHR [95% CI] =1.39 [1.05-1.81], P=0.02) increased the risk of TB recurrence. Prolonged treatment was associated with reduced TB recurrence (aHR [95% CI] =0.73 [0.61-0.88], P=0.001).
CONCLUSIONS: Recurrence remains a problem for successfully treated patients with sputum smear-positive pulmonary TB, especially those with independent risk factors. Further analysis of prolonged treatment is required.

DOI: 10.1016/j.cmi.2021.09.022
PMID: 34601149

68. **TCA cycle remodeling drives proinflammatory signaling in humans with pulmonary tuberculosis.**

PLoS Pathog. 2021 Sep 24;17(9):e1009941. doi: 10.1371/journal.ppat.1009941. eCollection 2021 Sep.

Collins JM(1), Jones DP(1), Sharma A(2), Khadka M(3), Liu KH(1), Kempker RR(1), Prideaux B(4), Maner-Smith K(3), Tukvadze N(5), Shah NS(1)(6)(7), Brust JCM(8), Sékaly RP(2), Gandhi NR(1)(6)(7), Blumberg HM(1)(6)(7), Ortlund EA(3), Ziegler TR(1)(9).

The metabolic signaling pathways that drive pathologic tissue inflammation and damage in humans with pulmonary tuberculosis (TB) are not well understood. Using combined methods in plasma high-resolution metabolomics, lipidomics and cytokine profiling from a multicohort study of humans with pulmonary TB disease, we discovered that IL-1β-mediated inflammatory signaling was closely associated with TCA cycle remodeling, characterized by accumulation of the proinflammatory metabolite succinate and decreased concentrations of the anti-inflammatory metabolite itaconate. This inflammatory metabolic response was particularly active in persons with multidrug-resistant (MDR)-TB that received at least 2 months of ineffective treatment and was only reversed after 1 year of appropriate anti-TB chemotherapy. Both succinate and IL-1β were significantly associated with proinflammatory lipid signaling, including increases in the products of phospholipase A2, increased arachidonic acid formation, and metabolism of arachidonic acid to proinflammatory eicosanoids. Together, these results indicate that decreased itaconate and accumulation of succinate and other TCA cycle intermediates is associated with IL-1β-mediated proinflammatory eicosanoid signaling in pulmonary TB disease. These findings support host metabolic remodeling as a key driver of pathologic inflammation in human TB disease.

DOI: 10.1371/journal.ppat.1009941
PMCID: PMC8494353
PMID: 34559866

69. **Molecular insights into the differential efflux mechanism of Rv1634 protein, a multidrug transporter of major facilitator superfamily in Mycobacterium tuberculosis.**

Proteins. 2021 Oct 3. doi: 10.1002/prot.26253. Online ahead of print.

Singh G(1), Akhter Y(1).

Currently, multidrug-resistant tuberculosis (MDR-TB) is a public health crisis and a major health security threat globally. In Mycobacterium tuberculosis (Mtb), major facilitator superfamily (MFS) is the largest group of secondary active transporters. Along with the transport of their natural substrates, MFS proteins were involved in a dynamic drug efflux mechanism that ultimately results in resistance against anti-TB drugs in Mtb. In the present study, the three-dimensional structure model of an MFS protein, Rv1634, a probable multidrug transporter from Mtb, was generated using homology modeling. The protein structure model was found in inward-open conformation having fourteen transmembrane helices. In addition, a central transport channel was deduced across the protein, and a single binding pocket was identified halfway through the central cavity by structural alignment with the homologous protein structures. Further, Rv1634 protein was studied based on the differential structural behavior of apo and ligand-bound forms. All the protein systems were inserted into a phospholipid bilayer to characterize the conformational dynamics of the protein using molecular dynamics (MD) simulations. Detailed analysis of the MD trajectories showed the diverse substrate specificity of the binding pocket for the antibiotics that caused differential movement in the ciprofloxacin and norfloxacin, to which Mtb strains have now become resistant. The expulsion of the drugs outside the bacterial cell occurs through the alternating-access mechanism of N and C-terminal domains, which is intriguing and essential to understanding the drug resistance mechanism in pathogenic bacteria. This article is protected by copyright. All rights reserved.

DOI: 10.1002/prot.26253
PMID: 34601761

70. **The Transcription Factor Rv1453 Regulates the Expression of qor and Confers Resistant to Clofazimine in Mycobacterium tuberculosis.**

Infect Drug Resist. 2021 Sep 24;14:3937-3948. doi: 10.2147/IDR.S324043. eCollection 2021.

Li Y(1), Fu L(1), Zhang W(1), Chen X(1), Lu Y(1).

OBJECTIVE: Clofazimine plays an important role in the treatment of drug-resistant tuberculosis. However, the mechanism of clofazimine resistance remains unclear. In order to slow down the occurrence of clofazimine resistance, it is necessary to study its resistance mechanism.
METHODS: In this study, we constructed Rv1453 knockout, complementary and overexpressed strain. The minimum inhibitory concentration (MIC) of clofazimine against Mycobacterium tuberculosis was detected by microplate alamar blue assay (MABA). The transcription levels of Rv1453 and its adjacent genes were detected by quantitative reverse transcriptase PCR. The purified Rv1453 protein was used for electrophoretic mobility shift assay (EMSA) to identify the binding site of Rv1453 protein.
RESULTS: The minimum inhibitory concentration (MIC) of clofazimine increased about 4-fold for the Rv1453 knockout strain and decreased about 4-fold for the Rv1453 overexpressed strain compared with Mycobacterium tuberculosis H37Rv. Further analysis showed that Rv1453 protein, as a regulatory protein, binds to the RNA polymerase binding site of qor and blocks the transcription process.
CONCLUSION: This study preliminarily revealed that Rv1453 protein of Mycobacterium tuberculosis affects its susceptibility to clofazimine by regulating the transcription level of qor, which is shedding a new light on the mechanism of clofazimine resistance.

DOI: 10.2147/IDR.S324043
PMCID: PMC8478341
PMID: 34594117

71. **Phylogenomic analysis and Mycobacterium tuberculosis antibiotic resistance prediction by whole-genome sequencing from clinical isolates of Caldas, Colombia.**

PLoS One. 2021 Oct 7;16(10):e0258402. doi: 10.1371/journal.pone.0258402. eCollection 2021.

Sánchez-Corrales L(1), Tovar-Aguirre OL(2), Galeano-Vanegas NF(3)(4), Castaño

Jiménez PA(2), Martínez-Vega RA(5), Maldonado-Londoño CE(6), Hernández-Botero JS(7)(8), Siller-López F(2)(9).

Mycobacterium tuberculosis (M. tuberculosis) was the pathogen responsible for the highest number of deaths from infectious diseases in the world, before the arrival of the COVID-19 pandemic. Whole genome sequencing (WGS) has contributed to the understanding of genetic diversity, the mechanisms involved in drug resistance and the transmission dynamics of this pathogen. The object of this study is to use WGS for the epidemiological and molecular characterization of M. tuberculosis clinical strains from Chinchiná, Caldas, a small town in Colombia with a high incidence of TB. Sputum samples were obtained during the first semester of 2020 from six patients and cultured in solid Löwenstein-Jensen medium. DNA extraction was obtained from positive culture samples and WGS was performed with the Illumina HiSeq 2500 platform for subsequent bioinformatic analysis. M. tuberculosis isolates were typified as Euro-American lineage 4 with a predominance of the Harlem and LAM sublineages. All samples were proven sensitive to antituberculosis drugs by genomic analysis, although no phenotype antimicrobial tests were performed on the samples, unreported mutations were identified that could require further analysis. The present study provides preliminary data for the construction of a genomic database line and the follow-up of lineages in this region.

DOI: 10.1371/journal.pone.0258402
PMCID: PMC8496870
PMID: 34618869 [Indexed for MEDLINE]

72. **The incalculable costs of tuberculosis.**

Lancet Glob Health. 2021 Oct;9(10):e1337-e1338. doi: 10.1016/S2214-109X(21)00345-4. Epub 2021 Sep 3.

Cox H(1), Furin J(2).

Comment on
Lancet Glob Health. 2021 Oct;9(10):e1372-e1379.

DOI: 10.1016/S2214-109X(21)00345-4
PMID: 34487684 [Indexed for MEDLINE]

73. **Diagnostic Accuracy of Pyrazinamide Susceptibility Testing in Mycobacterium tuberculosis: A Systematic Review with Meta-Analysis.**

Microb Drug Resist. 2021 Sep 28. doi: 10.1089/mdr.2021.0048. Online ahead of print.

Bagheri M(1), Pormohammad A(2), Fardsanei F(3), Yadegari A(4), Arshadi M(5), Deihim B(6), Hajikhani B(7), Turner RJ(2), Khalili F(1), Mousavi SMJ(7), Dadashi M(8), Goudarzi M(7), Dabiri H(7), Goudarzi H(7), Mirsaeidi M(9), Nasiri MJ(7).

Introduction: Pyrazinamide (PZA) susceptibility testing plays a critical role in determining the appropriate treatment regimens for multidrug-resistant tuberculosis. We conducted a systematic review and meta-analysis to evaluate the diagnostic accuracy of sequencing PZA susceptibility tests against culture-based susceptibility testing methods as the reference standard. Methods: We searched the MEDLINE/PubMed, Embase, and Web of Science databases for the relevant records. The QUADAS-2 tool was used to assess the quality of the studies. Diagnostic accuracy measures (i.e., sensitivity and specificity) were pooled with a random-effects model. All statistical analyses were performed with Meta-DiSc (version 1.4, Cochrane Colloquium, Barcelona, Spain), STATA (version 14, Stata Corporation, College Station, TX), and RevMan (version 5.3, The Nordic Cochrane Centre, the Cochrane Collaboration, Copenhagen, Denmark) software. Results: A total of 72 articles, published between 2000 and 2019, comprising data for 8,701 isolates of Mycobacterium tuberculosis were included in the final analysis. The pooled sensitivity and specificity of the PZA sequencing test against all reference tests (the combination of BACTEC mycobacteria growth indicator tube 960 (MGIT 960), BACTEC 460, and proportion method) were 87% (95% CI: 85-88) and 94.7% (95% CI: 94-95). The positive likelihood ratio, negative likelihood ratio, diagnostic odds ratio, and the area under the curve estimates were found to be 12.0 (95% CI: 9.0-16.0), 0.17 (95% CI: 0.13-0.21), 106 (95% CI: 71-158), and 96%, respectively. Deek's test result indicated a low likelihood for publication bias (p = 0.01). Conclusions: Our analysis indicated that PZA sequencing may be used in combination with conventional tests due to the advantage of the time to result and in scenarios where culture tests are not feasible. Further work to improve molecular tests would benefit from the availability of standardized reference standards and improvements to the methodology.

DOI: 10.1089/mdr.2021.0048
PMID: 34582723

74. **iAtbP-Hyb-EnC: Prediction of antitubercular peptides via heterogeneous feature representation and genetic algorithm based ensemble learning model.**

Comput Biol Med. 2021 Oct;137:104778. doi: 10.1016/j.compbiomed.2021.104778. Epub 2021 Aug 25.

Akbar S(1), Ahmad A(2), Hayat M(3), Rehman AU(4), Khan S(5), Ali F(6).

Tuberculosis (TB) is a worldwide illness caused by the bacteria Mycobacterium tuberculosis. Owing to the high prevalence of multidrug-resistant tuberculosis, numerous traditional strategies for developing novel alternative therapies have been presented. The effectiveness and dependability of these procedures are not always consistent. Peptide-based therapy has recently been regarded as a preferable alternative due to its excellent selectivity in targeting specific cells without affecting the normal cells. However, due to the rapid growth of the peptide samples, predicting TB accurately has become a challenging task. To effectively identify antitubercular peptides, an intelligent and reliable prediction model is indispensable. An ensemble learning approach was used in this study to improve expected results by compensating for the shortcomings of individual classification algorithms. Initially, three distinct representation approaches were used to formulate the training samples: k-space amino acid composition, composite physiochemical properties, and one-hot encoding. The feature vectors of the applied feature extraction methods are then combined to generate a heterogeneous vector. Finally, utilizing individual and heterogeneous vectors, five distinct nature classification models were used to evaluate prediction rates. In addition, a genetic algorithm-based ensemble model was used to improve the suggested model's prediction and training capabilities. Using Training and independent datasets, the proposed ensemble model achieved an accuracy of 94.47% and 92.68%, respectively. It was observed that our proposed "iAtbP-Hyb-EnC" model outperformed and reported ~10% highest training accuracy than existing predictors. The "iAtbP-Hyb-EnC" model is suggested to be a reliable tool for scientists and might play a valuable role in academic research and drug discovery. The source code and all datasets are publicly available at https://github.com/Farman335/iAtbP-Hyb-EnC.

DOI: 10.1016/j.compbiomed.2021.104778
PMID: 34481183 [Indexed for MEDLINE]

75. **Identification of novel benzothiopyranones with ester and amide motifs derived from active metabolite as promising leads against Mycobacterium tuberculosis.**

Eur J Med Chem. 2021 Oct 15;222:113603. doi: 10.1016/j.ejmech.2021.113603. Epub 2021 Jun 5.

Li P(1), Wang B(2), Fu L(2), Guo K(3), Ma C(3), Wang B(3), Lin Z(1), Li G(4),

Huang H(5), Lu Y(6).

We reported three distinct series of novel benzothiopyranones, derived from an active metabolite (M-1) of anti-TB agent 6b. These small molecules were evaluated for their biological activities against a range of Mycobacterium tuberculosis (M. tuberculosis) strains. Preliminary druggability evaluation demonstrated that M-1 showed good aqueous solubility and hepatocyte stability. Benzothiopyranones with acyl, sulfonyl and phosphoryl groups exhibited potent in vitro inhibitory activity against M. tuberculosis H37Rv and low cytotoxicity. In particular, compound 3d, containing a benzoate fragment, displayed marked metabolic stability and potent in vitro activity against drug-resistant tuberculosis clinical strains. Further druggability evaluation based on the identified compounds 3d, 4e and 5b is ongoing for the discovery of promising anti-TB agents.

DOI: 10.1016/j.ejmech.2021.113603
PMID: 34126456 [Indexed for MEDLINE]

76. **Mycobacterium enoyl acyl carrier protein reductase (InhA): A key target for antitubercular drug discovery.**

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Prasad MS(1), Bhole RP(2), Khedekar PB(3), Chikhale RV(4).

Enoyl acyl carrier protein reductase (InhA) is a key enzyme involved in fatty acid synthesis mainly mycolic acid biosynthesis that is a part of NADH dependent acyl carrier protein reductase family. The aim of the present literature is to underline the different scaffolds or enzyme inhibitors that inhibit mycolic acid biosynthesis mainly cell wall synthesis by inhibiting enzyme InhA. Various scaffolds were identified based on the screening technologies like high throughput screening, encoded library technology, fragment-based screening. The compounds studied include indirect inhibitors (Isoniazid, Ethionamide, Prothionamide) and direct inhibitors (Triclosan/Diphenyl ethers, Pyrrolidine Carboxamides, Pyrroles, Acetamides, Thiadiazoles, Triazoles) with better efficacy against drug resistance. Out of the several scaffolds studied, pyrrolidine carboxamides were found to be the best molecules targeting InhA having good bioavailability properties and better MIC. This review provides with a detailed information, analysis, structure activity relationship and useful insight on various scaffolds as InhA inhibitors.

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77. **Correction: Characteristics of pulmonary multidrug-resistant tuberculosis patients in Tigray Region, Ethiopia: A cross-sectional study.**

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Welekidan LN, Skjerve E, Dejene TA, Gebremichael MW, Brynildsrud O, Agdestein A, Tessema GT, Tønjum T, Yimer SA.

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