Literature

1. Bedaquiline.

Drugs and Lactation Database (LactMed) [Internet]. Bethesda (MD): National Library of Medicine (US); 2006–.
2022 Aug 15.

Data from two women taking bedaquiline and one of their breastfed infants indicate that exposure of the infant to the drug via breastmilk is substantial, with one infant having a therapeutic serum level. The clinical consequences of this exposure are unknown. The drug could protect the infant from multidrug-resistant tuberculosis, or could result in adverse effects. If bedaquiline is required by the mother, it is not a reason to discontinue breastfeeding. Monitor breastfed infants for adverse reactions, such as inadequate weight gain, liver toxicity, nausea, arthralgia, headache, hemoptysis, and chest pain.[1]

PMID: 31038856

2. **The incidence of TB and MDR-TB in pediatrics and therapeutic options: a systematic review.**

Syst Rev. 2022 Aug 4;11(1):157. doi: 10.1186/s13643-022-02023-1.

Harichander S(1), Wiafe E(2)(3), Mensah KB(2), Bangalee V(2), Oosthuizen F(2)(4).

BACKGROUND: Tuberculosis (TB) is considered one of the top 10 causes of death worldwide and the leading cause of death from a single infectious agent. Multidrug-resistant (MDR) TB can affect people of all age groups, including children (aged 0-15 years). However, very little is known about the extent of this problem in children. This systematic review aims to investigate the incidence of TB and drug-resistant (DR) TB among the pediatric population. It also reviews the therapeutic options available to treat the condition.
METHODS: A comprehensive search for all relevant evidence was conducted. The following databases were searched: MEDLINE, CINAHL, and Web of Science. The searched time frame was limited from January 1990 to December 2020 with a focus on the incidence of TB and MDR-TB among pediatrics and the therapeutic options available.
RESULTS: A total of 537 articles were obtained via the selected databases. After title and abstract screening, 418 articles were excluded leaving 119 articles. Full-text screening was conducted on 119 articles, excluding a further 110

articles. Thus, 9 articles were subject to quality assessment and included in this review. The 9 articles represented the age group of 0-15 years and included both males and females. All studies included were of retrospective study design.
DISCUSSION: The included studies mentioned a moderate increase in TB cases among pediatrics exacerbated by malnutrition, lack of bacille Calmette-Guérin (BCG) vaccination, and human immunodeficiency virus (HIV) coinfection. MDR-TB prevalence was especially high in South Africa. Drug therapy for both TB and MDR-TB yielded favorable outcomes among pediatrics. However, one of the biggest challenges with drug therapy includes the dosage forms available.
SYSTEMATIC REVIEW REGISTRATION: DOI: 10.17605/OSF.IO/G34NF.

DOI: 10.1186/s13643-022-02023-1
PMCID: PMC9354367
PMID: 35927752 [Indexed for MEDLINE]

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

3. **Bedaquiline-based treatment for extensively drug-resistant tuberculosis in South Africa: A cost-effectiveness analysis.**

PLoS One. 2022 Aug 5;17(8):e0272770. doi: 10.1371/journal.pone.0272770. eCollection 2022.

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

BACKGROUND: The treatment success rate of conventional anti-tuberculosis (TB) regimens for extensively drug-resistant TB (XDR-TB) is low, resulting in high morbidity and healthcare cost especially in the high TB burden countries. Recent clinical findings reported improved treatment outcomes of XDR-TB with the bedaquiline (BDQ)-based regimens. We aimed to evaluate the cost-effectiveness of BDQ-based treatment for XDR-TB from the perspective of the South Africa national healthcare provider.
METHODS: A 2-year decision-analytic model was designed to evaluate the clinical and economic outcomes of a hypothetical cohort of adult XDR-TB patients with (1) BDQ-based regimen and (2) injectable-based conventional regimen. The model inputs were retrieved from literature and public data. Base-case analysis and sensitivity analysis were performed. The primary model outputs included TB-related direct medical cost and disability-adjusted life years (DALYs).
RESULTS: In the base-case analysis, the BDQ group reduced 4.4152 DALYs with an incremental cost of USD1,606 when compared to the conventional group. The

incremental cost per DALY averted (ICER) by the BDQ group was 364 USD/DALY averted. No influential factor was identified in the sensitivity analysis. In probabilistic sensitivity analysis, the BDQ group was accepted as cost-effective in 97.82% of the 10,000 simulations at a willingness-to-pay threshold of 5,656 USD/DALY averted (1× gross domestic product per capita in South Africa). CONCLUSION: The BDQ-based therapy appeared to be cost-effective and showed a high probability to be accepted as the preferred cost-effective option for active XDR-TB treatment.

DOI: 10.1371/journal.pone.0272770
PMCID: PMC9355220
PMID: 35930574 [Indexed for MEDLINE]

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

4. **Feasibility and acceptability of asynchronous VOT among patients with MDR-TB.**

Int J Tuberc Lung Dis. 2022 Aug 1;26(8):760-765. doi: 10.5588/ijtld.21.0632.

Casalme DJO(1), Marcelo DB(1), Dela Cuesta DM(1), Tonquin M(1), Frias MVG(1), Gler MT(1).

BACKGROUND: We conducted a feasibility and acceptability study of video-observed therapy (VOT) among patients with multidrug-resistant TB (MDR-TB) and other types of drug-resistant TB (DR-TB) in the Philippines.METHODS: Patients aged ≥13 years were approached to use VOT. A smartphone with VOT mobile application to video-record medication intake was provided. Healthcare workers (HCWs) monitored adherence by watching videos via a web-based dashboard. Good adherence was defined as intake of >90% of expected doses. Feasibility and acceptability were assessed using a semi-structured questionnaire on a Likert scale.RESULTS: Of 308 patients, 110 (36%) patients chose VOT; 67 completed treatment using VOT and 43 stopped VOT prior to treatment outcome; 74/110 (67%) had good adherence. The treatment success rate was 88% and the loss to follow-up rate was 8.1%. Among HCWs, 90% (9/10) had a positive perception of VOT. All HCWs agreed that VOT data accurately reflect medication intake of the patients; 88/89 (99%) mentioned benefits of VOT, notably convenience, sense of comfort, privacy and security.CONCLUSIONS: VOT is feasible and acceptable for both patients and HCWs. This study could provide guidance to the country programme to launch VOT for treatment of patients with MDR-TB and other DR-TB.

DOI: 10.5588/ijtld.21.0632
PMID: 35898139 [Indexed for MEDLINE]

5. **Treatment and outcomes of multidrug-resistant tuberculosis in Auckland, 1995-2018.**

Intern Med J. 2022 Aug;52(8):1381-1386. doi: 10.1111/imj.15341. Epub 2022 May 31.

Cutfield T(1)(2)(3), Mowlem L(2), Paynter J(2), Christmas T(2), Harrison A(2), Lewis C(2), Newton S(4), Nisbet M(1)(2).

BACKGROUND: New Zealand has a low burden of tuberculosis; however, multidrug-resistant tuberculosis (MDR-TB) still represents a challenge for clinicians. This is the first description of clinical aspects of MDR-TB in New Zealand.
AIMS: To evaluate the treatment and outcomes of patients with MDR-TB disease in Auckland. Secondary aims were to review the incidence and clinical characteristics of MDR-TB disease.
METHODS: Clinical data were obtained for patients treated for MDR-TB at Auckland District Health Board (ADHB).
RESULTS: There were 60 patients nationally with MDR-TB between 1989 and 2018; 41 (69%) of 60 patients received care at ADHB. Pulmonary infection was present in 36 (88%) of 41 patients, with 19 (46%) of 41 patients with smear-positive sputum (smear 1-2+ in 6/41, 15%; smear 3-4+ in 13/41, 32%). The median duration of treatment was 22 months (range 7.5-26) for 18 (44%) of 41 patients who completed MDR-TB treatment by August 2018. The median duration of amikacin treatment was 6 months (range 2-12) for the 23 (61%) of 38 patients in whom these data were available. All 38 patients who received treatment for MDR-TB experienced adverse effects, most commonly gastrointestinal (66%), neurological (50%), ototoxicity (47%) and psychiatric (37%). Complications of intravenous access were experienced by 10 (27%) of 37 patients. Of the 19 (46%) of 41 patients who completed treatment, 18 (95%) achieved cure. There was one case who had recurrence because of inadequate treatment, and one case who had spontaneous resolution without treatment. Seventeen (41%) patients left Auckland prior to completion of treatment, mostly to return to their country of origin (15/17, 88%).
CONCLUSION: MDR-TB is uncommon in New Zealand. Treatment is frequently associated with adverse events; however, rates of cure for people completing treatment in New Zealand are high.

DOI: 10.1111/imj.15341
PMID: 33961727 [Indexed for MEDLINE]

6. **Letter from Thailand.**

Respirology. 2022 Aug;27(8):669-670. doi: 10.1111/resp.14317. Epub 2022 Jun 23.

Nana A(1)(2)(3), Chierakul N(4)(5).

DOI: 10.1111/resp.14317
PMID: 35738669 [Indexed for MEDLINE]

7. **Changes to treatment of drug-resistant tuberculosis.**

Lancet Infect Dis. 2022 Aug;22(8):1123. doi: 10.1016/S1473-3099(22)00460-1.

Venkatesan P.

DOI: 10.1016/S1473-3099(22)00460-1
PMID: 35870461 [Indexed for MEDLINE]

8. **Decreasing trend of drug-resistant TB in Italy.**

Int J Tuberc Lung Dis. 2022 Aug 1;26(8):775-783. doi: 10.5588/ijtld.22.0050.

Giannoni F(1), Lanni A(1), Iacobino A(1), Cirillo DM(2), Borroni E(2), Fattorini L(1).

BACKGROUND: TB caused by rifampicin-resistant (RR) and multidrug-resistant (MDR) Mycobacterium tuberculosis strains is a major concern to TB control globally. However, in the European Union, MDR-TB notifications among all bacteriologically confirmed TB cases with available drug susceptibility testing (DST) results decreased over the last years.METHODS: We conducted a retrospective analysis on DST results reported from 2011 to 2020 by 46 laboratories in 19 out of 20 regions in Italy in order to evaluate resistance trends to first- and second-line drugs in MDR/RR-TB strains isolated from Italian-born persons (IBPs) and foreign-born persons (FBPs).RESULTS: Of 23,972 M. tuberculosis strains examined (15,519 from FBPs and 8,453 from IBPs), MDR-TB decreased from 3.2% in 2011 to 2.2% in 2020. High MDR/RR-TB rates occurred mostly in FBPs from former Soviet Union countries. In 2017, a MDR/RR-TB increase was detected in FBPs from sub-Saharan Africa. MDR-TB strains showed consistent increase in resistance to pyrazinamide (PZA), slight increase in resistance to fluoroquinolones and a decrease in resistance to other drugs.CONCLUSION: While MDR/RR-TB cases slightly

decreased, a worrisome increase of resistance to PZA and fluoroquinolones among MDR/RR-TB patients was seen. This implies that a fast and efficient diagnosis aligned with therapy is crucial for TB control.

DOI: 10.5588/ijtld.22.0050
PMID: 35898124 [Indexed for MEDLINE]

9. **Disadvantage and the Experience of Treatment for Multidrug-Resistant Tuberculosis (MDR-TB).**

SSM Qual Res Health. 2022 Dec;2:100042. doi: 10.1016/j.ssmqr.2022.100042. Epub 2022 Jan 28.

Taylor HA(1), Dowdy DW(2), Searle AR(3), Stennett AL(3), Dukhanin V(1), Zwerling AA(4), Merritt MW(5).

DOI: 10.1016/j.ssmqr.2022.100042
PMCID: PMC8896740
PMID: 35252955

Conflict of interest statement: Declarations of Conflicts of Interest: None

10. **Prothionamide Dose Optimization Using Population Pharmacokinetics for Multidrug-Resistant Tuberculosis Patients.**

Antimicrob Agents Chemother. 2022 Aug 8:e0189321. doi: 10.1128/aac.01893-21. Online ahead of print.

Yun HY(#)(1), Chang MJ(#)(2)(3)(4), Jung H(#)(5), Chang V(6), Wang Q(6), Strydom N(6), Yoon YR(7)(8), Savic RM(6).

Prothionamide, a second-line drug for multidrug-resistant tuberculosis (MDR-TB), has been in use for a few decades. However, its pharmacokinetic (PK) profile remains unclear. This study aimed to develop a population PK model for prothionamide and then apply the model to determine the optimal dosing regimen for MDR-TB patients. Multiple plasma samples were collected from 27 MDR-TB patients who had been treated with prothionamide at 2 different study hospitals. Prothionamide was administered according to the weight-band dose regimen (500 mg/day for weight <50 kg and 750 mg/day for weight >50 kg) recommended by the World Health Organization. The population PK model was developed using nonlinear mixed-effects modeling. The probability of target attainment, based on systemic exposure and MIC, was used as a response target. Fixed-dose regimens

(500 or 750 mg/day) were simulated to compare the efficacies of various dosing regimens. PK profiles adequately described the two-compartment model with first-order elimination and the transit absorption compartment model with allometric scaling on clearance. All dosing regimens had effectiveness >90% for MIC values <0.4 μg/mL in 1.0-log kill target. However, a fixed dose of 750 mg/day was the only regimen that achieved the target resistance suppression of ≥90% for MIC values of <0.2 μg/mL. In conclusion, fixed-dose prothionamide (750 mg/day), regardless of weight-band, was appropriate for adult MDR-TB patients with weights of 40 to 67 kg.

DOI: 10.1128/aac.01893-21
PMID: 35938799

11. **24 loci MIRU-VNTR analysis and pattern of drug resistance in pre-extensively drug resistant pulmonary tuberculosis in Bangladesh.**

Infect Genet Evol. 2022 Aug;102:105304. doi: 10.1016/j.meegid.2022.105304. Epub 2022 May 18.

Monir BB(1), Sultana SS(2), Tarafder S(3).

Phylogenetic diversity and distinct phylogeographic distribution of Mycobacterium tuberculosis (MTB) contribute to regional differences in drug resistance. The emergence of pre-extensively drug resistant tuberculosis (Pre-XDR-TB) becomes obstacles to achieve End TB strategy in Bangladesh. This cross-sectional study was conducted to identify the strains of different lineages of MTB, their variations of distribution among Pre-XDR-TB cases and to observe the linkage of particular strains of MTB with drug resistance. A total of 33 Pre-XDR-TB isolates were enrolled in this study. All isolates were confirmed as MTB by MPT 64 antigen detection and genotyped by 24 loci Mycobacterial Interspersed Repetitive Unit-Variable Number of Tandem Repeats (MIRU-VNTR) analysis. Drug resistance was detected by second line Line probe assay (LPA). Beijing was the predominant strain 16 (48.48%), followed by Delhi/CAS 5(15.15%), LAM 4 (12.12%) and Harlem 3(9.10%), EAI 2(6.06%), Cameroon 2(6.06%) and NEW-1 1(3.03%). There were 31 different genotypes consisting of 2 clusters and 29 singletons. All the clustered strains were belonged to Beijing lineage. Recent transmission occurred manly by Beijing strains, showed low transmission rate (12.1%). Of 33 isolates 30(90.90%) were Fluoroquinolones resistant, the mutations involved was Asp94Gly in gyr A MUT 3C gene 13(39.39%) in quinolone resistance determining region (QRDR) followed by 11 (33.33%) in gyr A MUT 1. Three (9.10%) isolates showed resistant to injectable 2nd line drugs and all mutation occurs in G1484T of rrs MUT 2. Beijing lineage was predominant in treatment failure and relapse cases. Levofloxacin was resistant to all

Pre-XDR-TB cases, but moxifloxacin showed low level resistance. QUB 26 was the most discriminatory locus (0.85) among 24 loci whereas MIRU 2 was the least (0.03). 24 loci MIRU-VNTR analysis shows high discriminatory index (0.71), found to be powerful tool for genotyping of Pre-XDR-TB, which is the first study in Bangladesh that enhanced the current TB control policy.

DOI: 10.1016/j.meegid.2022.105304
PMID: 35595025 [Indexed for MEDLINE]

12. **Bedaquiline exposure in pregnancy and breastfeeding in women with rifampicin-resistant tuberculosis.**

Br J Clin Pharmacol. 2022 Aug;88(8):3548-3558. doi: 10.1111/bcp.15380. Epub 2022 May 26.

Court R(1)(2), Gausi K(1), Mkhize B(1), Wiesner L(1), Waitt C(3), McIlleron H(1)(2), Maartens G(1)(2), Denti P(1), Loveday M(4)(5).

AIMS: We aimed to explore the effect of pregnancy on bedaquiline pharmacokinetics (PK) and describe bedaquiline exposure in the breast milk of mothers treated for rifampicin-resistant tuberculosis (TB), where there are no human data available.
METHODS: We performed a longitudinal PK study in pregnant women treated for rifampicin-resistant TB to explore the effect of pregnancy on bedaquiline exposure. Pharmacokinetic sampling was performed at 4 time-points over 6 hours in the third trimester, and again at approximately 6 weeks postpartum. We obtained serial breast milk samples from breastfeeding mothers, and a single plasma sample taken from breastfed and nonbreastfed infants to assess bedaquiline exposure. We used liquid chromatography-tandem mass spectrometry to perform the breast milk and plasma bedaquiline assays, and population PK modelling to interpret the bedaquiline concentrations.
RESULTS: We recruited 13 women, 6 of whom completed the ante- and postpartum PK sampling. All participants were HIV-positive on antiretroviral therapy. We observed lower ante- and postpartum bedaquiline exposures than reported in nonpregnant controls. Bedaquiline concentrations in breast milk were higher than maternal plasma (milk to maternal plasma ratio: 14:1). A single random plasma bedaquiline and M2 concentration was available in 4 infants (median age: 6.5 wk): concentrations in the 1 breastfed infant were similar to maternal plasma concentrations; concentrations in the 3 nonbreastfed infants were detectable but lower than maternal plasma concentrations.
CONCLUSION: We report low exposure of bedaquiline in pregnant women treated for

rifampicin-resistant TB. Bedaquiline significantly accumulates in breast milk; breastfed infants receive mg/kg doses of bedaquiline equivalent to maternal doses.

DOI: 10.1111/bcp.15380
PMCID: PMC9296589
PMID: 35526837 [Indexed for MEDLINE]

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

13. **Recent advances in oxazolidinones as antituberculosis agents.**

Future Med Chem. 2022 Aug;14(15):1149-1165. doi: 10.4155/fmc-2022-0079. Epub 2022 Jul 22.

Lu H(1), Wang H(1), Zhao H(1), Zhang D(1).

Tuberculosis (TB) is an infectious and fatal disease caused by Mycobacterium tuberculosis (Mtb) and remains a serious public health threat; therefore, the development of new antitubercular agents is a priority for the World Health Organization's End TB strategy and the United Nations' Sustainable Development Goals to eradicate TB. Oxazolidinones are a class of synthetic antibacterial agents with a distinct mode of action developed for the treatment of Gram-positive bacterial infections. Many oxazolidinones exhibit good activity against Mtb, and some are currently in clinical trials for multidrug-resistant TB and extensively drug-resistant TB therapy. In this review, the mechanism of action, activity and toxicity of oxazolidinones and recent progress in the research and development of oxazolidinones as anti-TB agents are summarized.

DOI: 10.4155/fmc-2022-0079
PMID: 35866418 [Indexed for MEDLINE]

14. **Pediatric DR-TB: A Neglected Epidemic.**

Indian J Pediatr. 2022 Sep;89(9):927. doi: 10.1007/s12098-022-04290-1. Epub 2022 Jul 4.

Gupta S(1)(2), Verma AK(3), Kant S(3).

DOI: 10.1007/s12098-022-04290-1
PMID: 35781616 [Indexed for MEDLINE]

15. **Emerging threat of drug-resistant tuberculosis and trends in the era of COVID-19: A descriptive study from northwestern Nigeria.**

J Clin Tuberc Other Mycobact Dis. 2022 May 17;28:100319. doi: 10.1016/j.jctube.2022.100319. eCollection 2022 Aug.

Muhammad Dayyab F(1), Iliyasu G(2), Garba Ahmad B(3), Aliyu Umar I(4), Musa Shuaib N(5), Bajehson M(6), Muhammad Daiyab I(7), Akpala O(1), Remilekun O(1), Garba Habib A(2); For Kano TB Concilium Experts.

BACKGROUND: Mycobacterium tuberculosis with resistance to first line and second line anti tuberculous drugs is a serious setback in the treatment of tuberculosis (TB). The COVID-19 pandemic constitutes a serious threat that could unwind the recent gains made thus far in the control of tuberculosis. This study aims to explore the pattern of drug resistant tuberculosis (DRTB) in our institution. We also aimed to explore the changing trends of TB in the era of the COVID-19 pandemic.
METHODS: This descriptive study included all DRTB patients admitted and managed in the hospital between January 2018 and December 2020. We compare TB case detection in the facility before and after COVID-19 pandemic. Drug susceptibility testing were expressed as frequencies and percentages.
RESULTS: The study found that there was 66.03%, 45.09% and 77.78% drop in case detection of drug-sensitive TB (DSTB), DRTB and Fluoroquinolone (FQ) resistant TB respectively in the year 2020 compared to 2019. The drop in cases was similar when the year 2020 was compared to 2018. Among the 132 patients in the cohort, resistance to isoniazid, fluoroquinolones and second-line injectable agents were reported as 23.48%, 12.88%, and 31.06% respectively.
CONCLUSION: We question the potential reason why a drop in tuberculosis cases was observed in the year 2020 and we alert the Nigerian authorities that COVID-19 control efforts going hand-in-hand with intensified TB case finding and surveillance efforts and initiating proper TB treatment for persons with active TB are urgently needed.

DOI: 10.1016/j.jctube.2022.100319
PMCID: PMC9110314
PMID: 35599722

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

16. **Treatment outcomes of multidrug-resistant tuberculosis with chronic kidney/liver disease.**

Eur Respir J. 2022 Aug 10;60(2):2200930. doi: 10.1183/13993003.00930-2022. Print 2022 Aug.

Chung C(1)(2), Shin JE(1)(2), Jeon D(3), Kang H(4), Yim JJ(5), Jo KW(1), Shim TS(6).

DOI: 10.1183/13993003.00930-2022
PMID: 35710263 [Indexed for MEDLINE]

Conflict of interest statement: Conflict of interest: Jae-Joon Yim received donations of linezolid (Zyvox) from Pfizer, Inc., and delamanid (Deltyba) from Otsuka Pharmaceutical Co. for the clinical trials for which he served as a principal investigator. All other authors report no potential conflicts of interest.

17. **Laboratory-based study of drug resistance and genotypic profile of multidrug-resistant tuberculosis isolates in Salvador, Bahia, Brazil.**

Rev Soc Bras Med Trop. 2022 Jul 25;55:e00132022. doi: 10.1590/0037-8682-0013-2022. eCollection 2022.

Sousa EO(1)(2), Carneiro RTO(2), Montes FCOF(3), Conceição EC(4), Bartholomay P(5), Marinho JM(6), Lima KVB(7), Natividade MSD(8), Araújo WN(5), Matos ED(6), Barbosa T(2)(9).

BACKGROUND: Surveillance of multidrug resistant/extensively drug-resistant tuberculosis (MDR/XDR-TB) is essential to guide disease dissemination control measures. Brazil contributes to a significant fraction of tuberculosis (TB) cases worldwide, but only few reports addressed MDR/XDR-TB in the country. METHODS: This cross-sectional, laboratory-based study describes the phenotypic resistance profiles of isolates obtained between January 2008 and December 2011 in Bahia, Brazil, and sociodemographic, epidemiological, and clinical characteristics (obtained from mandatory national registries) of the corresponding 204 MDR/XDR-TB patients. We analyzed the mycobacterial spoligotyping and variable number of tandem repeats of mycobacterial

interspersed repetitive units in 12-loci profiles obtained from Salvador.
RESULTS: MDR/XDR-TB patients were predominantly male, had a median age of 43 years, belonged to black ethnicity, and failed treatment before MDR-TB diagnosis. Nearly one-third of the isolates had phenotypic resistance (evaluated by mycobacteria growth indicator tube assay) to second-line anti-TB drugs (64/204, 31%), of which 22% cases (14/64) were diagnosed as XDR-TB. Death was a frequent outcome among these individuals and was associated with resistance to second-line anti-TB drugs. Most isolates successfully genotyped belonged to the Latin-American Mediterranean (LAM) Family, with an unprecedented high proportion of LAM10-Cameroon subfamily bacilli. More than half of these isolates were assigned to a unique cluster by the genotyping methods performed. Large clusters of identical genotypes were also observed among LAM SIT42 and SIT376 strains.
CONCLUSIONS: We highlight the need for strengthening local and national efforts to perform early detection of TB drug resistance and to prevent treatment discontinuation to limit the emergence of drug-resistant strains.

DOI: 10.1590/0037-8682-0013-2022
PMCID: PMC9359346
PMID: 35894395 [Indexed for MEDLINE]

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

18. **Systematic evaluation of line probe assays for the diagnosis of tuberculosis and drug-resistant tuberculosis.**

Clin Chim Acta. 2022 Aug 1;533:183-218. doi: 10.1016/j.cca.2022.06.020. Epub 2022 Jul 2.

Lin M(1), Chen YW(2), Li YR(2), Long LJ(3), Qi LY(4), Cui TT(5), Wu SY(2), Lin JY(6), Wu T(6), Yang YC(6), Yuan WH(2), Wu GY(2), Lan QW(7), Liu JQ(2), Li YP(8), Yu ZY(9), Guo XG(10).

BACKGROUND: Line probe assays (LPAs) are PCR-based assays used for the rapid diagnosis of Mycobacterium tuberculosis (MTB) and drug-resistant tuberculosis (DR-TB). But studies on its performance are insufficient. Thus, in this study, we conducted a systematic review and meta-analysis to evaluate the effect of LPAs in the detection of MTB and drug-resistant TB in comparison with the traditional culture and DST methods.
METHODS: A systemic literature search was conducted on the Web of Science, Embase, PubMed, the Cochrane Library, Scopus, and OVID databases. All the included studies were classified according to different detecting objects. Sensitivity, specificity, Positive Likely Ratio (PLR), Negative Likely Ratio

(NLR), Diagnostic Odds Ratio (DOR), corresponding 95% confidence interval, Area Under Curve (AUC), Deeks' funnel plot, and Bivariate Boxplot was used to do the evaluation.
RESULTS: 147 studies included 491 datasets, with 182,448 samples, were incorporated into our analysis. The sensitivity (95% CI), specificity (95% CI), PLR, NLR, DOR and AUC for MTB were 0.89 (0.86 to 0.92), 0.94 (0.90 to 0.97), 15.70, 0.11, 139 and 0.96, respectively; for rifampicin-resistant TB were 0.96 (0.95 to 0.97), 0.99 (0.98 to 0.99), 82.9, 0.04, 1994 and 1.00, respectively; for isoniazid-resistant TB were 0.91 (0.89 to 0.93), 0.99 (0.98 to 0.99), 83.4, 0.09, (0.99 to 1.00), 195.7, 0.07, 2783 and 1.00, respectively; for Multi-drug resistant TB (MDR-TB) were 0.93 (0.90 to 0.95), 1.00 (0.99 to 1.00), 195.7, 0.07, 2783 and 1.00, respectively; for extensively drug-resistant TB (XDR-TB) were 0.60 (0.33 to 0.82), 1.00 (0.95 to 1.00), 291.3, 0.4, 726 and 0.95, respectively; for (second-line drug-resistant TB) SLID-TB were 0.83 (0.78 to 0.87), 0.98 (0.97 to 0.99), 44.6, 0.17, 262 and 0.98, respectively. Sensitivity in pre-extensively drug-resistant TB (Pre-XDR-TB) was 0.67, specificity was 0.91. No publication bias existed according to Deeks' funnel plot.
CONCLUSION: High diagnosis performance was confirmed in LPAs for the diagnosis of MTB and drug-resistant TB. LPAs might be a good alternative to culture and DST in detecting MTB, RR-TB, INH-TB, XDR-TB, SLID-TB, and MDR-TB. While more studies were still needed to explore the diagnosis performance of LPAs for Pre-XDR TB.

DOI: 10.1016/j.cca.2022.06.020
PMID: 35792161 [Indexed for MEDLINE]

19. **Linezolid Exposure Is Associated with Cytopenias in Patients Treated for Multidrug-Resistant Tuberculosis.**

Antimicrob Agents Chemother. 2022 Aug 2:e0040822. doi: 10.1128/aac.00408-22. Online ahead of print.

Graciaa DS(1), Kipiani M(2), Magee MJ(3)(4), Mikiashvili L(2), Barbakadze K(2), Bablishvili N(2), Auld SC(4)(5), Alghamdi WA(6), Alshaer MH(7), Peloquin CA(7), Avaliani Z(2), Blumberg HM(1)(3)(4), Kempker RR(1).

Although linezolid is effective for multidrug-resistant TB (MDR-TB) tuberculosis treatment, it is associated with cytopenias after 4 weeks of administration. Data on toxicities with long-term use of linezolid and drug pharmacodynamics in MDR-TB treatment are limited, and concerns about toxicity present barriers to wider implementation. This was a secondary analysis of a prospective cohort

study of patients treated for MDR-TB in the country of Georgia from 2015 to 2017. Intensive blood sampling 4 to 6 weeks after treatment initiation with linezolid 600 mg daily was performed for pharmacokinetic (PK) analysis, including linezolid trough concentration (Cmin) and area under the curve from 0 to 24 hours (AUC0-24). Linezolid exposure was defined using literature-reported thresholds. Cytopenias were defined using an NIH adverse event (AE) scale. Logistic regression was used to evaluate the relationship between linezolid exposure and cytopenias. Among 76 patients receiving linezolid in their baseline treatment regimen and who had PK data available, cytopenia AEs occurred in 30 (39.5%) for an incidence rate of 46 per 100 person-years. The median duration of linezolid therapy was 526 days. No patients required dose reduction or interruption due to cytopenias. Median linezolid Cmin was 0.235 mg/L (interquartile range [IQR], 0.069 to 0.529), and median AUC0-24 was 89.6 mg·h/L (IQR, 69.2 to 116.2). Cytopenias were associated with linezolid PK parameters (Cmin > 2 mg/L and AUC0-24 > 160 mg·h/L). Cytopenias occurred frequently with long-term use of linezolid 600 mg/day and were associated with PK parameters but did not result in the need for treatment interruption in the management of a cohort of patients with MDR-TB.

DOI: 10.1128/aac.00408-22
PMID: 35916515

20. **Discovery and preclinical profile of sudapyridine (WX-081), a novel anti-tuberculosis agent.**

Bioorg Med Chem Lett. 2022 Sep 1;71:128824. doi: 10.1016/j.bmcl.2022.128824. Epub 2022 May 27.

Huang Z(1), Luo W(1), Xu D(2), Guo F(2), Yang M(2), Zhu Y(2), Shen L(2), Chen S(2), Tang D(1), Li L(3), Li Y(3), Wang B(4), Franzblau SG(5), Ding CZ(6).

Multidrug resistant tuberculosis (MDR-TB) remains a major human health challenge. Bedaquiline was approved in 2012 by the US FDA, and listed by WHO as a treatment for multidrug-resistant tuberculosis (MDR-TB) in 2018. However, the side effects of bedaquiline including the risk of unexplained mortality, QTc prolongation and hepatotoxicity limit its wide clinical use. Based on bedaquiline, we describe herein discovery and development of a novel diarylpyridine series, which led to identification of WX-081 (sudapyridine, 21l). It displayed excellent anti-mycobacterial activity against M. tuberculosis H37Rv in vitro and in vivo and low cytotoxicity; additionally WX-081 had excellent pharmacokinetic parameters in animals, better lung exposure and lower QTc prolongation potential compared to bedaquiline. WX-081 is currently under clinical phase II development (NCT04608955).

DOI: 10.1016/j.bmcl.2022.128824
PMID: 35636648 [Indexed for MEDLINE]

21. **Bedaquiline and Linezolid improve anti-TB treatment outcome in drug-resistant TB patients with HIV: A systematic review and meta-analysis.**

Pharmacol Res. 2022 Aug;182:106336. doi: 10.1016/j.phrs.2022.106336. Epub 2022 Jun 30.

Wu Y(1), Zhang Y(2), Wang Y(1), Wei J(3), Wang W(1), Duan W(1), Tian Y(1), Ren M(1), Li Z(3), Wang W(1), Zhang T(1), Wu H(1), Huang X(4).

OBJECTIVES: We aimed to assess the effect of second-line anti-TB treatment and determine which drugs can achieve the greatest clinical benefit for DR-TB-HIV patients by comparing multiple chemotherapy regimens, to provide a basis for evidence-based practice.
METHODS: We searched three electronic databases (PubMed, Web of Science and Cochrane) for related English studies published since 2010. A random-effect model was used to estimate the pooled result for the treatment outcomes. Subgroup analysis based on possible factors, such as ART, baseline CD4 T-cell count, treatment regimens, and profiles of drug resistance, was also conducted to assess factors for favorable outcome. Outcomes were treatment success and mortality.
RESULTS: 38 studies, 40 cohorts with 9279 patients were included. The pooled treatment success, mortality, treatment failure, and default rates were 57.5 % (95 % CI 53.1-61.9), 21 % (95 % CI 17.8-24.6), 4.8 % (95 % CI 3.5-6.5), and 10.7 % (95 % CI 8.7-13.1), respectively, in patients with DR-TB and HIV co-infection. Subgroup analysis showed that BDQ and LZD based regimen, and ≥ 2 Group A drugs were associated with a higher treatment success rate. Besides, higher CD4 T-cell count at baseline was also correlated with higher treatment success rate, too.
CONCLUSIONS: Suboptimal anti-TB outcomes underlining the need to expand the application of effective drugs and better regimen in high HIV setting. BDQ and LZD based all-oral regimen and early ART could contribute to higher treatment success, particularly among XDR-TB-HIV patients. Given that all included studies were observational, our findings emphasize the need for high-quality studies to further investigate the optimal treatment regimen for DR-TB-HIV.

DOI: 10.1016/j.phrs.2022.106336

PMID: 35779814 [Indexed for MEDLINE]

22. **Magnitude of Mycobacterium tuberculosis, drug resistance and associated factors among presumptive tuberculosis patients at St. Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia.**

PLoS One. 2022 Aug 1;17(8):e0272459. doi: 10.1371/journal.pone.0272459. eCollection 2022.

Kassa M(1), Desta K(2), Ambachew R(1), Gebreyohannes Z(1), Gebreyohanns A(1), Zena N(1), Amare M(3), Zerihun B(3), Getu M(3), Gize A(1).

BACKGROUND: Mycobacterium tuberculosis (M. tuberculosis) remains one of the most significant causes of death and a major public health problem in the community. As a result, the aim of this study was to determine magnitude of Mycobacterium tuberculosis, its drug resistance, and associated factors among presumptive tuberculosis (TB) patients at St. Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia.
METHODS: Cross-sectional study was conducted at St. Paul's Hospital Millennium Medical College (SPHMMC), Addis Ababa, Ethiopia from January to July 2019. Demographic and clinical data were collected by structured questionnaire through face to face interview. Using microscopic examination and GeneXpert MTB/RIF assay and culturing in the Lowenstein-Jensen (LJ) culture media, we collected and analyzed both pulmonary and extra-pulmonary clinical samples. Data were analyzed by SPSS version 23. Binary logistic regression was done to identify the associated risk factors and p-value less than 0.05 was taken as significant association.
RESULTS: Of the total 436 respondents, 223(51%) were male. The mean ±SD age of the participants was 38±17years. Overall, 27/436(6.2%) of the participants had confirmed Mycobacterium tuberculosis using the GeneXpert MTB/RIF assay and LJ culture media, and two isolates were resistant to RIF and one to INH medication, with two (0.5%) being MDR-TB. MTB infection was associated with previous TB contact history, patient weight loss, and CD4+ T-cell counts of 200-350/mm3 of blood.
CONCLUSION: The magnitude of M. tuberculosis and MDR-TB in this study underscores the need for improved early case detection and management of MDR-TB in order to reduce transmission and patient suffering.

DOI: 10.1371/journal.pone.0272459
PMCID: PMC9342779
PMID: 35913968 [Indexed for MEDLINE]

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

interests exist.

23. **Discovery and preclinical evaluations of JBD0131, a novel nitrodihydro-imidazooxazole anti-tuberculosis agent.**

Bioorg Med Chem Lett. 2022 Sep 15;72:128871. doi: 10.1016/j.bmcl.2022.128871. Epub 2022 Jun 28.

Luo W(1), Huang Z(1), Xu D(2), Yang M(2), Zhu Y(2), Shen L(2), Chen S(2), Tao X(3), Bin W(4), Hu Y(1), Franzblau SG(5), Jiang N(6), Wei Y(7), Wei X(8), Ding CZ(9).

Multidrug-resistant pulmonary tuberculosis (MDR-TB) is a major health problem worldwide. The treatment for MDR-TB requires medications for a long duration (up to 20-24 months) with second-line drugs resulting in unfavorable outcomes. Nitroimidazoles are promising antimycobacterial agents known to inhibit both aerobic and anaerobic mycobacterial activity. Delamanid and pretomanid are two nitroimidazoles approved by the regulatory agencies for MDR-TB treatment. However, both agents possess unsatisfactory absorption and QTc prolongation. In our search for a safer nitroimidazole, we discovered JBD0131 (2). It exhibited excellent anti-mycobacterial activity against M. tuberculosis H37Rv in vitro and in vivo, improved PK and absorption, reduced QT prolongation potential of delamanid. JBD0131 is currently in clinical development in China for pulmonary tuberculosis (CTR20202308).

DOI: 10.1016/j.bmcl.2022.128871
PMID: 35777718 [Indexed for MEDLINE]

24. **Prediction of Mycobacterium tuberculosis drug resistance by nucleotide MALDI-TOF-MS.**

Int J Infect Dis. 2022 Aug;121:47-54. doi: 10.1016/j.ijid.2022.04.061. Epub 2022 May 4.

Wu X(1), Tan G(2), Yang J(1), Guo Y(1), Huang C(3), Sha W(4), Yu F(5).

OBJECTIVES: To evaluate the performance of nucleotide matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF-MS) in predicting the drug resistance of Mycobacterium tuberculosis.
METHODS: A total of 115 rifampin-resistant and 53 rifampin-susceptible

tuberculosis (TB) clinical isolates were randomly selected from TB strains stored at -80℃ in the clinical laboratory of Shanghai Pulmonary Hospital. Nucleotide MALDI-TOF-MS was performed to predict the drug resistance using phenotypic susceptibility as the gold standard.
RESULTS: The overall assay sensitivities and specificities of nucleotide MALDI-TOF-MS were 92.2% and 100.0% for rifampin, 90.9% and 98.6% for isoniazid, 71.4% and 81.2% for ethambutol, 85.1% and 93.1% for streptomycin, 94.0% and 100.0% for amikacin, 77.8% and 99.3% for kanamycin, 75.0% and 93.3% for ofloxacin, and 75.0% and 93.3% for moxifloxacin. The concordances between nucleotide MALDI-TOF-MS antimicrobial susceptibility testing (AST) and phenotypic AST were 94.6% (rifampin), 90.1% (isoniazid), 79.2% (ethambutol), 89.9% (streptomycin), 99.4% (amikacin), 97.0% (kanamycin), 88.1% (ofloxacin), and 88.0% (moxifloxacin).
CONCLUSION: Nucleotide MALDI-TOF-MS could be a promising tool for rapid detection of Mycobacterium tuberculosis drug sensitivity to rifampin, isoniazid, ethambutol, streptomycin, amikacin, kanamycin, ofloxacin, and moxifloxacin.

DOI: 10.1016/j.ijid.2022.04.061
PMID: 35523300 [Indexed for MEDLINE]

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

25. **Emerging impact of triazoles as anti-tubercular agent.**

Eur J Med Chem. 2022 Aug 5;238:114454. doi: 10.1016/j.ejmech.2022.114454. Epub 2022 May 13.

Sharma A(1), Agrahari AK(2), Rajkhowa S(3), Tiwari VK(4).

Tuberculosis, a disease of poverty is a communicable infection with a reasonably high mortality rate worldwide. 10 Million new cases of TB were reported with approx 1.4 million deaths in the year 2019. Due to the growing number of drug-sensitive and drug-resistant tuberculosis cases, there is a vital need to develop new and effective candidates useful to combat this deadly disease. Despite tremendous efforts to identify a mechanism-based novel antitubercular agent, only a few have entered into clinical trials in the last six decades. In recent years, triazoles have been well explored as the most valuable scaffolds in drug discovery and development. Triazole framework possesses favorable properties like hydrogen bonding, moderate dipole moment, enhanced water solubility, and also the ability to bind effectively with biomolecular targets

of M. tuberculosis and therefore this scaffold displayed excellent potency against TB. This review is an endeavor to summarize an up-to-date innovation of triazole-appended hybrids during the last 10 years having potential in vitro and in vivo antitubercular activity with structure activity relationship analysis. This review may help medicinal chemists to explore the triazole scaffolds for the rational design of potent drug candidates having better efficacy, improved selectivity and minimal toxicity so that these hybrid NCEs can effectively be explored as potential lead to fight against M. tuberculosis.

DOI: 10.1016/j.ejmech.2022.114454
PMID: 35597009 [Indexed for MEDLINE]

26. **Destroyed left lung due to multidrug-resistant Mycobacterium tuberculosis.**

Lancet Infect Dis. 2022 Aug;22(8):1252. doi: 10.1016/S1473-3099(22)00180-3.

Eskandari SK(1), Akkerman OW(2).

DOI: 10.1016/S1473-3099(22)00180-3
PMID: 35870469 [Indexed for MEDLINE]

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

27. **Synthesis and evaluation of inhibitors of Mycobacterium tuberculosis UGM using bioisosteric replacement.**

Bioorg Med Chem. 2022 Sep 1;69:116896. doi: 10.1016/j.bmc.2022.116896. Epub 2022 Jun 23.

Fu J(1), He Z(2), Fu H(3), Xia Y(2), N'Go I(4), Lou H(5), Wu J(2), Pan W(6), Vincent SP(7).

There is a dearth of tuberculosis (TB) drug development activity as current therapeutic treatments are inadequate due to the appearance of drug-resistant TB. The enzyme UDP-galactopyranose mutase (UGM) is involved in the biosynthesis of galactan which is essential for cell wall integrity and bacterial viability. Its inhibition has thus been featured as profitable strategy for anti-TB drug discovery. In this study, we report on the synthesis of amides derived from rosmarinic acid, their inhibitory effect towards purified UGM using three

distinct biochemical assays: FP, HPLC and SPR. The rosmarinic amides generally showed a significantly higher affinity for UGM than the corresponding rosmarinic ester. In particular, compound 5h displayed interesting binding affinity values (Kd = 58 ± 7, 63 ± 9 μM towards KpUGM and MtUGM respectively). Furthermore, a new UGM SPR assay was established and confirmed that 5h binds to UGM with a dissociation constant of 104.8 ± 6.5 μM. Collectively, this study validates the amide bioisosteric strategy which has been successfully implemented to develop UGM inhibitors from rosmarinic acid, providing a substantial basis for further design of novel UGM inhibitors and anti-mycobacterial agents.

DOI: 10.1016/j.bmc.2022.116896
PMID: 35777270 [Indexed for MEDLINE]

28. **The elimination of drug-resistant tuberculosis from a pulmonary resection surgery perspective.**

Int J Surg. 2022 Jul 31;104:106790. doi: 10.1016/j.ijsu.2022.106790. Online ahead of print.

Ghazvini K(1), Keikha M(2).

DOI: 10.1016/j.ijsu.2022.106790
PMID: 35918001

29. **Burden of tuberculosis and its association with socio-economic development status in 204 countries and territories, 1990-2019.**

Front Med (Lausanne). 2022 Jul 22;9:905245. doi: 10.3389/fmed.2022.905245. eCollection 2022.

Xue Y(1), Zhou J(2), Wang P(1), Lan JH(1), Lian WQ(1), Fan YY(1), Xu BN(3), Yin JP(4), Feng ZH(5), Zhou J(6), Jia CY(1).

BACKGROUND: Tuberculosis (TB) always runs in the forefront of the global burden when it comes to infectious diseases. Tuberculosis, which can lead to impairment of quality of life, financial hardship, discrimination, marginalization, and social barriers, is a major public health problem. The assessment of TB burden and trend can provide crucial information for policy decision and planning, and help countries in the world to achieve the goal of sustainable development of ending the epidemic of TB in 2030.

METHODS: All data are from the Global Burden of Disease 2019 (GBD 2019) database, which analyzed the burden trend of age-standardized incidence, DALYs, and deaths rate in TB and HIV/AIDS-infected TB over the past 30 years. Also, GBD 2019 not only analyzed the burden distribution of TB in 204 countries and main regions of the world but also analyzed the relationship between the burden of global TB and the socio-demographic Index (SDI).
RESULTS: The age-standardized incidence, age-standardized disability-adjusted life years (DALYs), and age-standardized deaths rate for HIV-negative TB were 10,671.45 (9,395.60-12,194.10), 59,042.45 (53,684.78-64,641.53), and 1,463.62 (1,339.24-1,602.71) (95% CI, per 100,000 person-years) in 2019, respectively. Age-standardized incidence, age-standardized DALYs, and age-standardized deaths rate of HIV/AIDS-XDR-TB (95% CI, per 1,000 person-years) were 2.10 (1.51-2.90), 64.23 (28.64-117.74), and 1.01 (0.42-1.86), respectively. We found that TB is inversely proportional to SDI, the age-standardized incidence, DALYs, and deaths rate low burden countries were in high SDI areas, while high burden countries were in low SDI areas. The global TB showed a slow decline trend, but the age-standardized incidence of HIV-positive TB was increasing, and mainly distributed in sub-Saharan Africa.
CONCLUSION: Age-standardized incidence, age-standardized DALYs, and age-standardized deaths rate of TB is related to SDI, and the burden of low SDI countries is lighter than that of high SDI countries. Without effective measures, it will be difficult for countries around the world to achieve the goal of ending the TB epidemic by 2030. Effective control of the spread of TB requires concerted efforts from all countries in the world, especially in the countries with low SDI, which need to improve the diagnosis and preventive measures of TB and improve the control of HIV/AIDS-TB.

DOI: 10.3389/fmed.2022.905245
PMCID: PMC9355511
PMID: 35935764

30. **Adjunctive Zoledronate + IL-2 administrations enhance anti-tuberculosis Vγ2Vδ2 T-effector populations, and improve treatment outcome of multidrug-resistant tuberculosis(1).**

Emerg Microbes Infect. 2022 Dec;11(1):1790-1805. doi: 10.1080/22221751.2022.2095930.

Shen H(1), Yang E(1)(2), Guo M(3), Yang R(1), Huang G(1), Peng Y(1), Sha W(1), Wang F(4), Shen L(2).

Multidrug-resistant tuberculosis (MDR-TB) is a refractory disease with high mortality rate due to no or few choices of antibiotics. Adjunctive immunotherapy may help improve treatment outcome of MDR-TB. Our decade-long studies demonstrated that phosphoantigen-specific Vγ2Vδ2 T cells play protective roles in immunity against TB. Here, we hypothesized that enhancing protective Vγ2Vδ2 T-effector cells could improve treatment outcome of MDR-TB. To address this, we employed clinically approved drugs Zoledronate (ZOL) and IL-2 to induce anti-TB Vγ2Vδ2 T-effector cells as adjunctive immunotherapy against MDR-TB infection of macaques. We found that adjunctive ZOL/IL-2 administrations during TB drugs treatment of MDR-TB-infected macaques significantly expanded Vγ2Vδ2 T cells and enhanced/sustained Vγ2Vδ2 T-effector subpopulation producing anti-TB cytokines until week 21. ZOL/IL-2 administrations, while expanding Vγ2Vδ2 T cells, significantly increased/sustained numbers of circulating CD4+ Th1 and CD8+ Th1-like effector populations, with some γδ T- or αβ T-effector populations trafficking to airway at week 3 until week 19 or 21 after MDR-TB infection. Adjunctive ZOL/IL-2 administrations after MDR-TB infection led to lower bacterial burdens in lungs than TB drugs alone, IL-2 alone or saline controls, and resulted in milder MDR-TB pathology/lesions. Thus, adjunctive Zoledronate + IL-2 administrations can enhance anti-TB Vγ2Vδ2 T- and αβ T-effector populations, and improve treatment outcome of MDR-TB.

DOI: 10.1080/22221751.2022.2095930
PMCID: PMC9310823
PMID: 35765887 [Indexed for MEDLINE]

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

31. **Rapid Diagnosis of XDR and Pre-XDR TB: A Systematic Review of Available Tools.**

Arch Bronconeumol. 2022 Jul 28:S0300-2896(22)00498-7. doi: 10.1016/j.arbres.2022.07.012. Online ahead of print.

[Article in English, Spanish]

Saderi L(1), Puci M(1), Di Lorenzo B(1), Centis R(2), D'Ambrosio L(3), Akkerman OW(4), Alffenaar JC(5), Caminero JA(6), Chakaya JM(7), Denholm JT(8), Kurhasani X(9), Ong CWM(10), Rendon A(11), Silva DR(12), Tiberi S(13), Zenner D(14), Cabibbe AM(15), Migliori GB(16), Sotgiu G(1).

INTRODUCTION: No previous systematic reviews have comprehensively investigated the features of Xpert MTB/XDR and other rapid tests to diagnose pre-XDR/XDR-TB. The aim of this systematic review is to assess existing rapid diagnostics for

pre-XDR/XDR-TB from a point-of-care perspective and describe their technical characteristics (i.e., sensitivity, specificity, positive and negative predictive values).
METHODS: Embase, PubMed, Scopus, and Web of Science were searched to detect the articles focused on the accuracy of commercially available rapid molecular diagnostic tests for XDR-TB according to PRISMA guidelines. The analysis compared the diagnostic techniques and approaches in terms of sensitivity, specificity, laboratory complexity, time to confirmed diagnosis.
RESULTS: Of 1298 records identified, after valuating article titles and abstracts, 97 (7.5%) records underwent full-text evaluation and 38 records met the inclusion criteria. Two rapid World Health Organization (WHO)-endorsed tests are available: Xpert MTB/XDR and GenoType MTBDRsl (VER1.0 and VER 2.0). Both tests had similar performance, slightly favouring Xpert, although only 2 studies were available (sensitivity 91.4-94; specificity 98.5-99; accuracy 97.2-97.7; PPV 88.9-99.1; NPV 95.8-98.9).
CONCLUSIONS: Xpert MTB/XDR could be suggested at near-point-of-care settings to be used primarily as a follow-on test for laboratory-confirmed TB, complementing existing rapid tests detecting at least rifampicin-resistance. Both Xpert MTB/XDR and GenoType MTBDRsl are presently diagnosing what WHO defined, in 2021, as pre-XDR-TB.

DOI: 10.1016/j.arbres.2022.07.012
PMID: 35945071

32. **Major revision version 11.0 of the European AIDS Clinical Society Guidelines 2021.**

HIV Med. 2022 Sep;23(8):849-858. doi: 10.1111/hiv.13268. Epub 2022 Mar 25.

Ryom L(1)(2), De Miguel R(3), Cotter AG(4)(5), Podlekareva D(1)(6), Beguelin C(7), Waalewijn H(8), Arribas JR(3), Mallon PWG(4)(5), Marzolini C(9)(10), Kirk O(1)(11), Bamford A(12), Rauch A(7), Molina JM(13), Kowalska JD(14), Guaraldi G(15), Winston A(16), Boesecke C(17), Cinque P(18), Welch S(19), Collins S(20), Behrens GMN(21)(22); EACS Governing Board.

BACKGROUND: The European AIDS Clinical Society (EACS) Guidelines were revised in 2021 for the 17th time with updates on all aspects of HIV care.
KEY POINTS OF THE GUIDELINES UPDATE: Version 11.0 of the Guidelines recommend six first-line treatment options for antiretroviral treatment (ART)-naïve adults: tenofovir-based backbone plus an unboosted integrase inhibitor or plus

doravirine; abacavir/lamivudine plus dolutegravir; or dual therapy with lamivudine or emtricitabine plus dolutegravir. Recommendations on preferred and alternative first-line combinations from birth to adolescence were included in the new paediatric section made with Penta. Long-acting cabotegravir plus rilpivirine was included as a switch option and, along with fostemsavir, was added to all drug-drug interaction (DDI) tables. Four new DDI tables for anti-tuberculosis drugs, anxiolytics, hormone replacement therapy and COVID-19 therapies were introduced, as well as guidance on screening and management of anxiety disorders, transgender health, sexual health for women and menopause. The sections on frailty, obesity and cancer were expanded, and recommendations for the management of people with diabetes and cardiovascular disease risk were revised extensively. Treatment of recently acquired hepatitis C is recommended with ongoing risk behaviour to reduce transmission. Bulevirtide was included as a treatment option for the hepatitis Delta virus. Drug-resistant tuberculosis guidance was adjusted in accordance with the 2020 World Health Organization recommendations. Finally, there is new guidance on COVID-19 management with a focus on continuance of HIV care.
CONCLUSIONS: In 2021, the EACS Guidelines were updated extensively and broadened to include new sections. The recommendations are available as a free app, in interactive web format and as an online pdf.

DOI: 10.1111/hiv.13268
PMID: 35338549 [Indexed for MEDLINE]

33. **Family directly observed therapy for children with drug-resistant TB.**

Int J Tuberc Lung Dis. 2022 Aug 1;26(8):792-794. doi: 10.5588/ijtld.22.0168.

Rekart ML(1), Morshed T(2), Mulanda WK(2), Klieascikova J(3), Sitali N(4), Rajabzoda A(5), Avzamova S(5), Pirmahmadzoda B(6), Aung A(2), Sayfulloev M(2), Sleit R(4), Sinha A(7).

DOI: 10.5588/ijtld.22.0168
PMCID: PMC9341496
PMID: 35898123 [Indexed for MEDLINE]

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

34. **High clustering rate and genotypic drug-susceptibility screening for the newly**

recommended anti-tuberculosis drugs among global extensively drug-resistant Mycobacterium tuberculosis isolates.

Emerg Microbes Infect. 2022 Dec;11(1):1857-1866. doi: 10.1080/22221751.2022.2099304.

Trisakul K(1)(2), Nonghanphithak D(1)(2), Chaiyachat P(1)(2), Kaewprasert O(1)(2), Sakmongkoljit K(3), Reechaipichitkul W(1)(2), Chaiprasert A(4), Blair D(5), Clark TG(6), Faksri K(1)(2).

Multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) make TB difficult to control. Global susceptibility data for six newly recommended anti-TB drugs against M/XDR-TB are still limited. Using publicly available whole-genome sequences, we determined the proportion of 513 phenotypically XDR-TB isolates that carried mutations associated with resistance against these drugs (bedaquiline, clofazimine, linezolid, delamanid, pretomanid and cycloserine). Mutations of Rv0678 and Rv1979c were detected in 69/513 isolates (13.5%) for bedaquiline resistance and 79/513 isolates (15.4%) for clofazimine resistance with additional mmpL5 mutations. Mutations conferring resistance to delamanid were detected in fbiB and ddn genes for 11/513 isolates (2.1%). For pretomanid, a mutation was detected in the ddn gene for 3/513 isolates (0.6%). Nineteen mutations of pykA, cycA, ald, and alr genes, conferring resistance to cycloserine, were found in 153/513 isolates (29.8%). No known mutations associated with linezolid resistance were detected. Cluster analysis showed that 408/513 isolates fell within 99 clusters and that 354 of these isolates were possible primary drug-resistant TB (292 XDR-TB, 57 pre-XDR-TB and 5 MDR-TB). Clonal transmission of primary XDR isolates might contribute significantly to the high prevalence of DR-TB globally.

DOI: 10.1080/22221751.2022.2099304
PMCID: PMC9336503
PMID: 35792049 [Indexed for MEDLINE]

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

35. **Diagnostic performance of the AID line probe assay in the detection of Mycobacterium tuberculosis and drug resistance in Romanian patients with presumed TB.**

PLoS One. 2022 Aug 10;17(8):e0271297. doi: 10.1371/journal.pone.0271297. eCollection 2022.

Rachow A(1)(2), Saathoff E(1)(2), Mindru R(3), Popescu O(3), Lugoji D(3), Mahler B(3), Merker M(4), Niemann S(4), Olaru ID(4)(5), Kastner S(1), Hoelscher M(1)(2), Lange C(4)(5)(6)(7), Ibraim E(3).

BACKGROUND: The AID line probe assay has shown promising evaluation data on the detection of Mycobacterium tuberculosis as well as 1st- and 2nd-line drug resistance, using isolates and selected clinical samples in previous studies.
METHODS: The diagnostic performance of three AID-modules (AID INH/RIF, AID FQ/EMB and AID AG) was analyzed in sputum samples from patients with presumed tuberculosis against culture methods and phenotypic drug resistance as reference standards.
RESULTS: 59 patients had culture-confirmed tuberculosis. All AID modules showed moderate sensitivity (46/59, 78.0%, 65.3-87.7) and very good specificity (100%, 95.5%, 93.7%). There was a high proportion of invalid tests, resulting in 32.6%, 78.3% and 19.6% of 46 AID-positive tuberculosis cases, who could not be assessed for drug resistance by the AID INH/RIF-, AID FQ/EM- and AID AG-module, respectively. A small number of patients showed drug resistance by reference standards: Three MDR-TB cases plus three, one and one patients with resistance to streptomycin, fluoroquinolones and aminoglycosides, respectively. The AID-assay detected all MDR-TB cases, two of three streptomycin-resistant TB cases, one of one of fluoroquinolone-resistant and missed one aminoglycoside-resistant TB case.
DISCUSSION: The high proportion of invalid results precludes the use of the AID-assay from direct sputum-based tuberculosis and drug-resistance testing.

DOI: 10.1371/journal.pone.0271297
PMCID: PMC9365181
PMID: 35947609 [Indexed for MEDLINE]

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

36. **Development and Validation of a Nomogram for the Prediction of Unfavorable Treatment Outcome Among Multi-Drug Resistant Tuberculosis Patients in North West Ethiopia: An Application of Prediction Modelling.**

Infect Drug Resist. 2022 Jul 21;15:3887-3904. doi: 10.2147/IDR.S372351. eCollection 2022.

Anley DT(1), Akalu TY(2), Merid MW(2), Tsegaye T(3).

BACKGROUND: Multidrug-resistant tuberculosis (MDR-TB) is a global problem and a health security threat, which makes "Ending the global TB epidemic in 2035"

unachievable. Globally, the unfavourable treatment outcome remains unacceptably high. Therefore, this study aimed to develop a risk prediction model for unfavorable treatment outcomes in MDR-TB patients, which can be used by clinicians as a simple clinical tool in their decision-making.
OBJECTIVE: The objective of this study was to develop and validate a risk prediction model for the prediction of unfavorable treatment outcomes among MDR-TB patients in North-West Ethiopia.
METHODS: We used MDR-TB data collected from the University of Gondar and Debre Markos referral hospitals. A retrospective follow-up study was conducted and a total of 517 patients were included in the study. STATA version 16 statistical software and R version 4.0.5 were used for the analysis. Descriptive statistics were carried out. A multivariable model was fitted using all potent predictors selected by the lasso regression method. A simplified risk prediction model (nomogram) was developed based on the binomial logit-based model, and its performance was described by assessing its discriminatory power and calibration. Finally, decision curve analysis (DCA) was done to evaluate the clinical and public health impact of the developed model.
RESULTS: The developed nomogram comprised six predictors: baseline anemia, major adverse event, comorbidity, age, marital status, and treatment supporter. The model has a discriminatory power of 0.753 (95% CI: 0.708, 0.798) and calibration test of (P-value = 0.695). It was internally validated by bootstrapping method, and it has a relatively corrected discrimination performance (AUC = 0.744, 95CI: 0.699, 0.788). The optimism coefficient was found to be 0.009. The decision curve analysis showed the net benefit of the model as threshold probabilities varied.
CONCLUSION: The developed nomogram can be used for individualized prediction of unfavorable treatment outcomes in MDR-TB patients for it has a satisfactory level of accuracy and good calibration. The model is clinically interpretable and was found to have added benefits in clinical practice.

DOI: 10.2147/IDR.S372351
PMCID: PMC9317379
PMID: 35903578

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

37. **Development and validation of a nomogram for the prediction of late culture conversion among multi-drug resistant tuberculosis patients in North West Ethiopia: An application of prediction modelling.**

PLoS One. 2022 Aug 10;17(8):e0272877. doi: 10.1371/journal.pone.0272877. eCollection 2022.

Anley DT(1), Akalu TY(2), Merid MW(2), Dessie AM(1), Zemene MA(1), Demissie B(1), Arage G(3).

INTRODUCTION: Multi-drug resistant tuberculosis has impeded tuberculosis prevention and control due to its low treatment efficiency and prolonged infectious periods. Early culture conversion status has long been used as a predictor of good treatment outcomes and an important infection control metric, as culture-negative patients are less likely to spread tuberculosis. There is also evidence that suggests that delayed sputum conversion is linked to negative outcomes. Therefore, this study was aimed at developing a nomogram to predict the risk of late culture conversion in patients with multi-drug resistant tuberculosis using readily available predictors.
OBJECTIVE: The objective of this study was to develop and validate a risk prediction nomogram for the prediction of late culture conversion among multi-drug resistant tuberculosis patients in North-West Ethiopia.
METHODS: Multi-drug resistant tuberculosis data from the University of Gondar and the Debre Markos referral hospitals have been used and a total of 316 patients were involved. The analysis was carried out using STATA version 16 and R version 4.0.5 statistical software. Based on the binomial logistic regression model, a validated simplified risk prediction model (nomogram) was built, and its performance was evaluated by assessing its discriminatory power and calibration. Finally, decision curve analysis (DCA) was used to assess the generated model's clinical and public health impact.
RESULTS: Registration group, HIV co-infection, baseline BMI, baseline sputum smear grade, and radiological abnormalities were prognostic determinants used in the construction of the nomogram. The model has a discriminating power of 0.725 (95% CI: 0.669, 0.781) and a P-value of 0.665 in the calibration test. It was internally validated using the bootstrapping method, and it was found to perform similarly to the model developed on the entire dataset. The decision curve analysis revealed that the model has better clinical and public health impact than other strategies specified.
CONCLUSION: The developed nomogram, which has a satisfactory level of accuracy and good calibration, can be utilized to predict late culture conversion in MDR-TB patients. The model has been found to be useful in clinical practice and is clinically interpretable.

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PMCID: PMC9365138
PMID: 35947625 [Indexed for MEDLINE]

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

interests exist.

38. **Prediction of drug resistance by Sanger sequencing of Mycobacterium tuberculosis complex strains isolated from multidrug resistant tuberculosis suspect patients in Ethiopia.**

PLoS One. 2022 Aug 5;17(8):e0271508. doi: 10.1371/journal.pone.0271508. eCollection 2022.

Mesfin EA(1), Merker M(2)(3), Beyene D(4), Tesfaye A(5), Shuaib YA(2)(6), Addise D(1), Tessema B(7), Niemann S(2)(8).

BACKGROUND: Ethiopia is one of the high multidrug-resistant tuberculosis (MDR-TB) burden countries. However, phenotypic drug susceptibility testing can take several weeks due to the slow growth of Mycobacterium tuberculosis complex (MTBC) strains. In this study, we assessed the performance of a Sanger sequencing approach to predict resistance against five anti-tuberculosis drugs and the pattern of resistance mediating mutations.
METHODS: We enrolled 226 MTBC culture-positive MDR-TB suspects and collected sputum specimens and socio-demographic and TB related data from each suspect between June 2015 and December 2016 in Addis Ababa, Ethiopia. Phenotypic drug susceptibility testing (pDST) for rifampicin, isoniazid, pyrazinamide, ethambutol, and streptomycin using BACTEC MGIT 960 was compared with the results of a Sanger sequencing analysis of seven resistance determining regions in the genes rpoB, katG, fabG-inhA, pncA, embB, rpsL, and rrs.
RESULT: DNA isolation for Sanger sequencing was successfully extracted from 92.5% (209/226) of the MTBC positive cultures, and the remaining 7.5% (17/226) strains were excluded from the final analysis. Based on pDST results, drug resistance proportions were as follows: isoniazid: 109/209 (52.2%), streptomycin: 93/209 (44.5%), rifampicin: 88/209 (42.1%), ethambutol: 74/209 (35.4%), and pyrazinamide: 69/209 (33.0%). Resistance against isoniazid was mainly mediated by the mutation katG S315T (97/209, 46.4%) and resistance against rifampicin by rpoB S531L (58/209, 27.8%). The dominating resistance-conferring mutations for ethambutol, streptomycin, and pyrazinamide affected codon 306 in embB (48/209, 21.1%), codon 88 in rpsL (43/209, 20.6%), and codon 65 in pncA (19/209, 9.1%), respectively. We observed a high agreement between phenotypic and genotypic DST, such as 89.9% (at 95% confidence interval [CI], 84.2%-95.8%) for isoniazid, 95.5% (95% CI, 91.2%-99.8%) for rifampicin, 98.6% (95% CI, 95.9-100%) for ethambutol, 91.3% (95% CI, 84.6-98.1%) for pyrazinamide and 57.0% (95% CI, 46.9%-67.1%) for streptomycin.
CONCLUSION: We detected canonical mutations implicated in resistance to rifampicin, isoniazid, pyrazinamide, ethambutol, and streptomycin. High agreement with phenotypic DST results for all drugs renders Sanger sequencing

promising to be performed as a complementary measure to routine phenotypic DST in Ethiopia. Sanger sequencing directly from sputum may accelerate accurate clinical decision-making in the future.

DOI: 10.1371/journal.pone.0271508
PMCID: PMC9355188
PMID: 35930613 [Indexed for MEDLINE]

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

39. **High fluoroquinolone resistance proportions among multidrug-resistant tuberculosis driven by dominant L2 Mycobacterium tuberculosis clones in the Mumbai Metropolitan Region.**

Genome Med. 2022 Aug 22;14(1):95. doi: 10.1186/s13073-022-01076-0.

Dreyer V(#)(1)(2), Mandal A(#)(3), Dev P(#)(3), Merker M(1)(4)(5), Barilar I(1), Utpatel C(1), Nilgiriwala K(3), Rodrigues C(6), Crook DW(5)(7); CRyPTIC Consortium, Rasigade JP(8)(9), Wirth T(10)(11), Mistry N(#)(3), Niemann S(#)(12)(13)(14).

BACKGROUND: Multidrug-resistant (MDR) Mycobacterium tuberculosis complex (MTBC) strains are a serious health problem in India, also contributing to one-fourth of the global MDR tuberculosis (TB) burden. About 36% of the MDR MTBC strains are reported fluoroquinolone (FQ) resistant leading to high pre-extensively drug-resistant (pre-XDR) and XDR-TB (further resistance against bedaquiline and/or linezolid) rates. Still, factors driving the MDR/pre-XDR epidemic in India are not well defined.
METHODS: In a retrospective study, we analyzed 1852 consecutive MTBC strains obtained from patients from a tertiary care hospital laboratory in Mumbai by whole genome sequencing (WGS). Univariate and multivariate statistics was used to investigate factors associated with pre-XDR. Core genome multi locus sequence typing, time scaled haplotypic density (THD) method and homoplasy analysis were used to analyze epidemiological success, and positive selection in different strain groups, respectively.
RESULTS: In total, 1016 MTBC strains were MDR, out of which 703 (69.2%) were pre-XDR and 45 (4.4%) were XDR. Cluster rates were high among MDR (57.8%) and pre-XDR/XDR (79%) strains with three dominant L2 (Beijing) strain clusters (Cl 1-3) representing half of the pre-XDR and 40% of the XDR-TB cases. L2 strains were associated with pre-XDR/XDR-TB ($P < 0.001$) and, particularly Cl 1-3 strains, had high first-line and FQ resistance rates (81.6-90.6%). Epidemic success analysis using THD showed that L2 strains outperformed L1, L3, and L4

strains in short- and long-term time scales. More importantly, L2 MDR and MDR + strains had higher THD success indices than their not-MDR counterparts. Overall, compensatory mutation rates were highest in L2 strains and positive selection was detected in genes of L2 strains associated with drug tolerance (prpB and ppsA) and virulence (Rv2828c). Compensatory mutations in L2 strains were associated with a threefold increase of THD indices, suggesting improved transmissibility.
CONCLUSIONS: Our data indicate a drastic increase of FQ resistance, as well as emerging bedaquiline resistance which endangers the success of newly endorsed MDR-TB treatment regimens. Rapid changes in treatment and control strategies are required to contain transmission of highly successful pre-XDR L2 strains in the Mumbai Metropolitan region but presumably also India-wide.

DOI: 10.1186/s13073-022-01076-0
PMID: 35989319

40. **Availability and costs of medicines for the treatment of tuberculosis in Europe.**

Clin Microbiol Infect. 2022 Aug 9:S1198-743X(22)00394-9. doi: 10.1016/j.cmi.2022.07.026. Online ahead of print.

Günther G(1), Guglielmetti L(2), Leu C(3), Lange C(4), van Leth F(5); for TBNET.

Collaborators: Hafizi H(6), Khachatryan N(7), Aroyan H(7), Kabasakalyan E(8), Knappik M(9), Skrahina A(10), Klimuk D(10), Nikolenka A(10), Muylle I(11), Milanov V(12), Velkovska D(13), Tarinska N(13), Bachiyska E(14), Jankovic M(15), Pieridou D(16), Adamide T(17), Nicolaou N(18), Vasakova M(19), Sukholytka M(19), Kopeckà E(19), Andersen ÅB(20), Folkvardsen DB(21), Svensson E(21), Danilovits M(22), Kummik T(23), Vasankari T(24), Fréchet-Jachym M(25), Nahmiash A(25), Togonidze T(26), Avaliani Z(26), Kinkladze I(26), Aspindzelashvili R(26), Bichashvili T(26), Losaberidze G(26), Merabishvili T(26), Kalsdorf B(27), Manika K(28), Tsiakitzis K(29), Bakos A(30), Ægisdóttir TR(31), Michelsen GS(31), Karlsdóttir K(31), McLaughlin AM(32), Fitzgibbon M(33), Chemtob D(34), Codecasa LR(35), Ferrarese M(35), Torri S(35), Gjocaj M(36), Kuksa L(37), Davidaviciene E(38), Wirtz G(39), Perrin M(40), Asciak AP(41), Chesov D(42), de Lange W(43), Akkerman O(43), Poposka BI(44), Mack U(45), Jensenius M(46), Kvalvik L(47), Mengshoel AT(48), Kruczak K(49), Duarte R(50), Ribeiro N(51), Ibraim E(52), Kaluzhenina A(53), Barkanova O(53), Pesut D(54), Solovic I(55), Svetina P(56), Souza-Galvão ML(57), Millet JP(58), Casas X(59), Vives M(59), Bruchfeld J(60), Dalemo P(61), Jonsson J(62), Aeschbacher K(63), Keller P(64), Özkara S(65), Tiberi S(66), Chen C(67), Terleeva Y(68), Dudnyk A(69).

OBJECTIVES: To evaluate the access to comprehensive diagnostics and novel anti-tuberculosis medicines in European countries.
METHODS: We investigated access to genotypic and phenotypic M. tuberculosis drug susceptibility testing, availability of anti-tuberculosis drugs and calculated cost of drugs and treatment regimens at major tuberculosis treatment centers in countries of the World Health Organization (WHO) European region where rates of drug-resistant tuberculosis are highest among all WHO regions. Results are stratified by middle-income and high-income countries.
RESULTS: Overall, 43 treatment centers in 43 countries participated in the study. For WHO Group A drugs, the frequency of countries with availability of phenotypic drug susceptibility testing was as follows: 30/40 (75%) for levofloxacin, 33/40 (82%) for moxifloxacin, 19/40 (48%) for bedaquiline and 29/40 (72%) for linezolid, respectively. Overall, 36/43 (84%) and 24/43 (56%) of countries had access to bedaquiline and delamanid, while only 6/43 (14%) had access to rifapentine. Treatment of patients with extensively drug-resistant tuberculosis with a regimen including a carbapenem was only available in 17/43 (40%) of the countries. Median cost of regimens for drug-susceptible tuberculosis, multidrug-resistant/rifampicin-resistant tuberculosis (shorter regimen, including bedaquiline for six months) and extensively drug-resistant tuberculosis (including bedaquiline, delamanid and a carbapenem) were € 44 (min-max € 15-152), € 764 (min-max € 542-15152) and € 8709 (min-max € 7965-11759) in middle-income countries (n=12), and € 280 (min-max-€78-1084), € 29765 (min-max 11116-40584), € 217591 (min-max € 82827-320146) in high-income countries (n=29).
CONCLUSION: In countries of the WHO Europe Region there is a widespread lack of drug susceptibility testing capacity to new and re-purposed anti-tuberculosis drugs, lack of access to essential medications in several countries and high treatment cost for drug-resistant tuberculosis.

DOI: 10.1016/j.cmi.2022.07.026
PMID: 35961488

41. **Population Pharmacokinetics of Delamanid and its Main Metabolite DM-6705 in Drug-Resistant Tuberculosis Patients Receiving Delamanid Alone or Coadministered with Bedaquiline.**

Clin Pharmacokinet. 2022 Aug;61(8):1177-1185. doi: 10.1007/s40262-022-01133-2. Epub 2022 Jun 7.

Tanneau L(1), Karlsson MO(1), Diacon AH(2), Shenje J(3), De Los Rios J(4),

Wiesner L(5), Upton CM(2), Dooley KE(6), Maartens G(5), Svensson EM(7)(8).

BACKGROUND AND OBJECTIVE: Delamanid is a nitroimidazole, a novel class of drug for treating tuberculosis, and is primarily metabolized by albumin into the metabolite DM-6705. The aims of this analysis were to develop a population pharmacokinetic (PK) model to characterize the concentration-time course of delamanid and DM-6705 in adults with drug-resistant tuberculosis and to explore a potential drug-drug interaction with bedaquiline when coadministered.
METHODS: Delamanid and DM-6705 concentrations after oral administration, from 52 participants (of whom 26 took bedaquiline concurrently and 20 were HIV-1 positive) enrolled in the DELIBERATE trial were analyzed using nonlinear mixed-effects modeling.
RESULTS: Delamanid PK were described by a one-compartment disposition model with transit compartment absorption (mean absorption time of 1.45 h [95% confidence interval 0.501-2.20]) and linear elimination, while the PK of DM-6705 metabolite were described by a one-compartment disposition model with delamanid clearance as input and linear elimination. Predicted terminal half-life values for delamanid and DM-6705 were 15.1 h and 7.8 days, respectively. The impact of plasma albumin concentrations on delamanid metabolism was not significant. Bedaquiline coadministration did not affect delamanid PK. Other than allometric scaling with body weight, no patients' demographics were significant (including HIV).
CONCLUSIONS: This is the first joint PK model of delamanid and its DM-6705 metabolite. As such, it can be utilized in future exposure-response or exposure-safety analyses. Importantly, albumin concentrations, bedaquiline coadministration, and HIV co-infection (dolutegravir coadministration) did not have an effect on delamanid and DM-6705 PK.

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PMCID: PMC9349160
PMID: 35668346 [Indexed for MEDLINE]

Conflict of interest statement: Conflicts of interest LT, MOK, AHD, JS, JDLR, LW, CMU, KED, GM, and EMS have no conflicts of interest to declare.

42. **Design, Synthesis, and Biological Evaluation of Pyrrole-2-carboxamide Derivatives as Mycobacterial Membrane Protein Large 3 Inhibitors for Treating Drug-Resistant Tuberculosis.**

J Med Chem. 2022 Aug 11;65(15):10534-10553. doi: 10.1021/acs.jmedchem.2c00718. Epub 2022 Aug 1.

Zhao H(1), Gao Y(1), Li W(2), Sheng L(3), Cui K(4), Wang B(5), Fu L(5), Gao M(1), Lin Z(1), Zou X(3), Jackson M(2), Huang H(1), Lu Y(5), Zhang D(1).

In this work, pyrrole-2-carboxamides were designed with a structure-guided strategy based on the crystal structure of MmpL3 and a pharmacophore model. The structure-activity relationship studies revealed that attaching phenyl and pyridyl groups with electron-withdrawing substituents to the pyrrole ring and attaching bulky substituents to the carboxamide greatly improved anti-TB activity. Most compounds showed potent anti-TB activity (MIC < 0.016 μg/mL) and low cytotoxicity (IC50 > 64 μg/mL). Compound 32 displayed excellent activity against drug-resistant tuberculosis, good microsomal stability, almost no inhibition of the hERG K+ channel, and good in vivo efficacy. Furthermore, the target of the pyrrole-2-carboxamides was identified by measuring their potency against M. smegmatis expressing wild-type and mutated variants of the mmpL3 gene from M. tuberculosis (mmpL3tb) and determining their effect on mycolic acid biosynthesis using a [14C] acetate metabolic labeling assay. The present study provides new MmpL3 inhibitors that are promising anti-TB agents.

DOI: 10.1021/acs.jmedchem.2c00718
PMCID: PMC9379527
PMID: 35915958 [Indexed for MEDLINE]

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

43. **Drug Resistance Patterns and Trends in Patients with Suspected Drug-Resistant Tuberculosis in Dalian, China: A Retrospective Study.**

Infect Drug Resist. 2022 Jul 30;15:4137-4147. doi: 10.2147/IDR.S373125. eCollection 2022.

Pan Y(1), Yu Y(1), Lu J(1), Yi Y(1), Dou X(1), Zhou L(1).

PURPOSE: The emergence of drug-resistant tuberculosis (DR-TB) represents a threat to the control of tuberculosis. This study aimed to estimate the patterns and trends of DR-TB in patients with suspected DR-TB. In addition, risk factors for multidrug-resistant tuberculosis (MDR-TB) were identified among suspected DR-TB patients in Dalian, China.
PATIENTS AND METHODS: A total of 5661 patients with suspected DR-TB from Jan 1, 2013 to Dec 31, 2020 were included in the final analysis. The resistance pattern of all resistant strains was determined by drug susceptibility testing (DST) using the conventional Lowenstein-Jensen Proportion Method (LJ). DR-TB trends

were estimated from 2013 to 2020. During the research period, the chi-square test was employed to analyze the significance of linear drug-resistance trends across time. Bivariate and multivariate logistic regression were performed to assess factors associated with MDR-TB.
RESULTS: From 2013 to 2020, the resistance rates of rifampicin (RFP) and isoniazid (INH) decreased significantly, whereas the resistance rates of ethambutol (EMB) and streptomycin (SM) increased in patients with suspected DR-TB. From 2013 to 2020, the prevalence of DR-TB decreased in all patients from 34.71% to 28.01% with an average annual decrease of 3.02%. Among new cases, from 2013 to 2020, the prevalence of DR-TB (from 26.67% to 24.75%), RFP-resistant TB (RR-TB) (from 15.09% to 3.00%) and MDR-TB (from 6.08% to 2.62%) showed a significant downward trend. Among patients with a previous treatment history, DR-TB (from 54.70% to 37.50%), RR-TB (from 44.16% to 11.49%) and MDR-TB (from 26.90% to 10.34%) showed a significant downward trend from 2013 to 2020. Males (AOR 1.28, 95% CI 1.035-1.585), patients 45 to 64 years of age (AOR 1.75, 95% CI 1.342-2.284), patients 65 years and older (AOR 1.65, 95% CI 1.293-2.104), rural residents (AOR 1.24, 95% CI 1.014-1.519) and a previous treatment history (AOR 3.94, 95% CI 3.275-4.741) were risk factors for MDR-TB.
CONCLUSION: The prevalence of DR-TB, RR-TB and MDR-TB was significantly reduced from 2013 to 2020. Considerable progress has been made in the prevention and treatment of DR-TB during this period. However, the increasing rate of drug resistance in EMB and SM should be taken seriously. Suspected DR-TB patients who are male, older than 45 years of age, live in rural areas, and have a history of TB treatment should be given priority by health care providers.

DOI: 10.2147/IDR.S373125
PMCID: PMC9348136
PMID: 35937782

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

44. **Anti-Tubercular Activity of Pyrazinamide Conjugates: Synthesis and Structure-Activity Relationship Studies.**

Mini Rev Med Chem. 2022 Aug 19. doi: 10.2174/1389557522666220819092431. Online ahead of print.

Wahan SK(1)(2), Sharma S(3), Chawla PA(1).

Tuberculosis (TB) is an airborne infection caused by the bacteria Mycobacterium

Tuberculosis (MTB). It mainly affects the lungs and causes severe coughing, fever, and chest pains. With the rising prevalence of drug-resistant and inactive Tuberculosis (TB), there is an essential need to discover more effective molecules capable of combating this heinous illness. Pyrazinamide is a first-line tuberculosis therapy that shortens prophylactic duration from twelve to six months. The majority of presently used tuberculosis medications were found by a mix of serendipity and innovative chemical alterations of an existing lead drug. Given that the majority of these discoveries occurred years ago, there is a definite need to use fresh methodologies and technology for discovery to meet the grave danger posed by tuberculosis and the rise of treatment resistance strains. Although current research has provided significant insight into TB transmission, diagnosis, and treatment in the last four years, much more progress is needed to successfully reduce tuberculosis prevalence and eventually eradicate it. The disease continues to be a public health concern, second only to HIV/AIDS in high fatality rates. This review focuses on current efforts to translate the antitubercular activity of all known pyrazinamide analogues and proposes a novel approach for developing new anti-tubercular drugs based on the fusion of pyrazinamide with various heterocyclic rings that shorten treatment for drug-sensitive and multidrug-resistant tuberculosis.

DOI: 10.2174/1389557522666220819092431
PMID: 35986542

45. **Recent advances in PLGA micro/nanoparticle delivery systems as novel therapeutic approach for drug-resistant tuberculosis.**

Front Bioeng Biotechnol. 2022 Jul 22;10:941077. doi: 10.3389/fbioe.2022.941077. eCollection 2022.

Shao L(1), Shen S(1), Liu H(1).

Tuberculosis is a severe infectious disease caused by Mycobacterium tuberculosis and is a significant public health concern globally. The World Health Organization (WHO) recommends a combination regimen of several drugs, such as rifampicin (RIF), isoniazid (INH), pyrazinamide (PZA), and ethambutol (ETB), to treat tuberculosis. However, these drugs have low plasma concentrations after oral administration and require multiple high doses, which may lead to the occurrence and development of drug-resistant tuberculosis. Micro/Nanotechnology drug delivery systems have considerable potential in treating drug-resistant tuberculosis, allowing the sustained release of the drug and delivery of the

drug to a specific target. These system properties could improve drug bioavailability, reduce the dose and frequency of administration, and solve the problem of non-adherence to the prescribed therapy. This study systematically reviewed the recent advances in PLGA micro/nanoparticle delivery systems as a novel therapeutic approach for drug-resistant tuberculosis.

DOI: 10.3389/fbioe.2022.941077
PMCID: PMC9355142
PMID: 35935487

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

46. **Immune Regulatory Effect of Osteopontin Gene Therapy in a Murine Model of Multidrug Resistant Pulmonary Tuberculosis.**

Hum Gene Ther. 2022 Aug 4. doi: 10.1089/hum.2022.030. Online ahead of print.

Hernández-Bazán S(1), Mata-Espinosa D(1), Lozano-Ordaz V(1), Ramos-Espinosa O(1), Barrios-Payán J(1), López-Casillas F(2), Hernández Pando R(1).

Tuberculosis (TB) has been for many years a major public health problem since treatment is long and sometimes ineffective favoring the increase of multidrug-resistant mycobacteria (MDR-TB). Gene therapy is a novel and effective tool to regulate immune responses. In this study we evaluated the therapeutic effect of an adenoviral vector codifying osteopontin (AdOPN), a molecule known for their roles to favor Th1 and Th17 type-cytokine expression which are crucial in TB containment. A single dose of AdOPN administration in BALB/c mice suffering late progressive pulmonary MDR-TB produced significant lower bacterial load and pneumonia, due to higher expression of IFN-γ, IL-12, and IL-17 in coexistence with increase of granulomas in number and size, resulting in higher survival, in contrast with mice treated with the control adenovirus that codify the green fluorescent protein (AdGFP). Combined therapy of AdOPN with a regimen of second line antibiotics produced a better control of bacterial load in lung during the first days of treatment, suggesting that AdOPN can shorten chemotherapy. Taken together, gene therapy with AdOPN leads to higher immune responses against TB infection, resulting in a new potential treatment against pulmonary TB that can co-adjuvant chemotherapy.

DOI: 10.1089/hum.2022.030

PMID: 35615876

47. **Impact of alcohol drinking and tobacco smoking on the drug-resistance of newly diagnosed tuberculosis: a retrospective cohort study in Shandong, China, during 2004-2020.**

BMJ Open. 2022 Jul 28;12(7):e059149. doi: 10.1136/bmjopen-2021-059149.

Song WM(#)(1)(2), Li SJ(#)(3), Liu JY(#)(4), Fu Q(5), Xu TT(1), Tao NN(1), Zhang QY(1)(2), Liu SQ(1)(2), An QQ(1)(2), Zhu XH(1), Liu Y(1), Yu CB(6), Li YF(7), Dong J(8), Li HC(9)(10)(11).

OBJECTIVES: To investigate the independent and collective impact of alcohol drinking and tobacco smoking on the drug-resistance of newly diagnosed tuberculosis (TB).
DESIGN: This was a retrospective cohort study.
SETTING: Shandong, China.
PARTICIPANTS: Patients with newly diagnosed TB from 1 January 2004 to 31 December 2020 were collected. Exclusive criteria: retreated cases; extrapulmonary tuberculosis; without information on drug susceptibility testing results, smoking or drinking habits; bacteriological identification as non-tuberculous mycobacteria.
PRIMARY AND SECONDARY OUTCOME MEASURES: Patients were classified into four groups including smokers only (G1), drinker only (G2), smoker +drinker (G3), non-smoker +non-drinker group (G0). We described the drug-resistant profiles, clinical factors and calculated the ORs of different drug-resistance among G1, G2, G3, compared with G0 through univariate and multivariate logistics regression models.
RESULTS: Of the 7996 TB cases enrolled, the proportions of G1, G2, G3 and G0 were 8.25%, 3.89%, 16.46% and 71.40%, respectively. The rates of drug-resistant (DR)-TB, mono-resistant TB, multidrug resistant (MDR)-TB, polydrug resistant TB in G1, G2, G3 and G0 were 19.24%/16.4%/17.33%/19.08%, 11.52%/8.68%/10.94%/11.63%, 3.03%/2.57%/2.96%/3.66% and 4.70%/4.82%/3.34%/4.08%, respectively. G3 had a higher risk of MDR1: isoniazid +rifampin (adjusted OR (aOR)=1.91, 95% CI: 1.036 to 3.532), but had a lower risk of DR-TB (aOR=0.84, 95% CI: 0.71 to 0.99), rifampin-related resistance (aOR=0.68, 95% CI: 0.49 to 0.93), streptomycin-related resistance (aOR=0.82, 95% CI: 0.68 to 0.99), ethambutol-related resistance (aOR=0.57, 95% CI: 0.34 to 0.95), MDR3: isoniazid +rifampin+streptomycin (aOR=0.41, 95% CI: 0.19 to 0.85), any isoniazid +streptomycin resistance (aOR=0.85, 95% CI: 0.71 to 1.00). However, there were no significant differences between G1 and G0, G2 and G0 in all drug-resistant subtypes. Those patients with cavity had a higher risk of DR-TB among G3 (OR=1.35, 95% CI: 1.01 to 1.81).

CONCLUSION: Although we did not found an independent impact of alcohol drinking or tobacco smoking on TB drug-resistance, respectively, these two habits had a combined effect on TB drug-resistance.

DOI: 10.1136/bmjopen-2021-059149
PMCID: PMC9341182
PMID: 35902191 [Indexed for MEDLINE]

Conflict of interest statement: Competing interests: None declared.

48. **Assessing physical and chemical properties of saliva among tuberculosis patients on anti-tuberculosis treatment - An observational study.**

J Clin Tuberc Other Mycobact Dis. 2022 Jun 22;28:100322. doi: 10.1016/j.jctube.2022.100322. eCollection 2022 Aug.

Gowdappa Doddawad V(1), Shivananda S(2), Madhu B(3), Gurupadayya BM(4), Vidya CS(5), Jayaraj BS(6).

BACKGROUND: Tuberculosis (TB) is one of the major systemic conditions which is a preventable and curable infection but remains a significant cause of death. The WHO, in its global plan to stop TB reports, that poor treatment has resulted in the evolution of Mycobacterium tuberculosis strains that do not respond to treatment with the standard first-line combination of anti- tuberculosis medicines, resulting in the emergence of multidrug-resistant tuberculosis in almost every country of the world.The present study was aimed to assess the physical and chemical property of stimulated and unstimulated saliva and identify if any association exist with alterations in taste perception in patients with antituberculosis medications.
METHODS: A total of 30 patients on anti-tuberculosis drugs were considered as cases and 30 healthy volunteers were considered as controls and included in the study. All study subjects were assessed for their physical property like flow rate, viscosity, pH and chemical property like sodium, potassium, calcium, phosphorous of stimulated and unstimulated saliva. All the subjects on Anti-tuberculosis drugs were assessed for change in taste perceptions using the standard questionnaire.
RESULTS: There is a significant decrease in the flow rate (0.34 ± 0.06) and pH (5.89 ± 0.37) of unstimulated saliva of patients and the flow rate (0.38 ± 0.07) and viscosity (1.34 ± 0.28) of stimulated saliva among the case group compare to the control group. All the electrolytes' concentrations such as sodium,

potassium, calcium, and phosphorous values were significantly altered in stimulated and unstimulated saliva of the case group compared to the control group in which p-value < 0.05 was considered.
CONCLUSION: There are significant changes in physical and chemical properties of both stimulated and unstimulated saliva which has an effect on taste perception inpatient with anti-tuberculosis medications. Hence, salivary flow rate, pH, viscosity, and salivary electrolytes of tuberculosis patients should be considered as important parameters in guiding the diet, so that there will be an improvement in their taste perception and medication protocol, thus maintaining their nutritional status which leads to improving their health.

DOI: 10.1016/j.jctube.2022.100322
PMCID: PMC9294525
PMID: 35865185

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

49. **Integrative analysis of clinical health records, imaging and pathogen genomics identifies personalized predictors of disease prognosis in tuberculosis.**

medRxiv. 2022 Jul 21:2022.07.20.22277862. doi: 10.1101/2022.07.20.22277862. Preprint.

Sambarey A, Smith K, Chung C, Arora HS, Yang Z, Agarwal P, Chandrasekaran S.

Tuberculosis (TB) afflicts over 10 million people every year and its global burden is projected to increase dramatically due to multidrug-resistant TB (MDR-TB). The Covid-19 pandemic has resulted in reduced access to TB diagnosis and treatment, reversing decades of progress in disease management globally. It is thus crucial to analyze real-world multi-domain information from patient health records to determine personalized predictors of TB treatment outcome and drug resistance. We conduct a retrospective analysis on electronic health records of 5060 TB patients spanning 10 countries with high burden of MDR-TB including Ukraine, Moldova, Belarus and India available on the NIAID-TB portals database. We analyze over 200 features across multiple host and pathogen modalities representing patient social demographics, disease presentations as seen in cChest X rays and CT scans, and genomic records with drug susceptibility features of the pathogen strain from each patient. Our machine learning model, built with diverse data modalities outperforms models built using each modality

alone in predicting treatment outcomes, with an accuracy of 81% and AUC of 0.768. We determine robust predictors across countries that are associated with unsuccessful treatmentclinical outcomes, and validate our predictions on new patient data from TB Portals. Our analysis of drug regimens and drug interactions suggests that synergistic drug combinations and those containing the drugs Bedaquiline, Levofloxacin, Clofazimine and Amoxicillin see more success in treating MDR and XDR TB. Features identified via chest imaging such as percentage of abnormal volume, size of lung cavitation and bronchial obstruction are associated significantly with pathogen genomic attributes of drug resistance. Increased disease severity was also observed in patients with lower BMI and with comorbidities. Our integrated multi-modal analysis thus revealed significant associations between radiological, microbiological, therapeutic, and demographic data modalities, providing a deeper understanding of personalized responses to aid in the clinical management of TB.

DOI: 10.1101/2022.07.20.22277862
PMCID: PMC9327630
PMID: 35898335

50. **One-pot synthesis of α-Linolenic acid nanoemulsion-templated drug-loaded silica mesocomposites as efficient bactericide against drug-resistant Mycobacterium tuberculosis.**

Eur J Pharm Sci. 2022 Sep 1;176:106261. doi: 10.1016/j.ejps.2022.106261. Epub 2022 Jul 15.

Zhu P(1), Cai L(1), Liu Q(2), Feng S(3), Ruan H(3), Zhang L(1), Zhou L(1), Jiang H(4), Wang H(5), Wang J(6), Chen J(7).

Nowadays, pathogenic infection has posed a severe threat to the public health and environmental sanitation, urging a continuous search of efficacious and safe bactericidal agents of various formulated forms. Here, a facile one-pot hydrothermal preparation of mesoporous silica nanoparticles using ultrasonication-assisted nanoemulsion of α-Linolenic acid (α-LA) as template was developed. The formed silica mesocomposite at water/fatty-acid surface provides an easy yet green synthesis route, which can be generalized for the further encapsulation of hydrophobic drugs such as antimycobacterial Rifampicin (RIF). The obtained α-LA nanoemulsion-templated silica nanoparticles (LNS NPs), with a weight content of ∼17% α-LA in the composite, showed apparent antibacterial effect against Staphylococcus aureus (S. aureus). By comparison, the removal of α-LA from the silica nanoparticles (LNS-1 NPs) resulted in the composite of enlarged pore size with negligible bactericidal activities. Notably, the Isoniazide (INH) and Rifampicin (RIF)-encapsulated LNS NPs exhibited outstanding

antimycobacterial activity against both drug-sensitive and drug-resistant Mycobacterium tuberculosis (M. tuberculosis). The obtained highly biocompatible, biosafe and low-energy consumptive α-LA-contained mesostructured silica-based bactericide holds promising therapeutic potentials to tackle the emerging drug-resistant infectious microbes.

DOI: 10.1016/j.ejps.2022.106261
PMID: 35840102 [Indexed for MEDLINE]

51. **Moxifloxacin concentration correlate with QTc interval in rifampicin-resistant tuberculosis patients on shorter treatment regimens.**

J Clin Tuberc Other Mycobact Dis. 2022 Jun 6;28:100320. doi: 10.1016/j.jctube.2022.100320. eCollection 2022 Aug.

Kusmiati T(1)(2)(3), Made Mertaniasih N(4)(3), Nugroho Eko Putranto J(5), Suprapti B(6), Luthfah N(5), Soedarsono S(2)(3), Koesoemoprodjo W(2), Prawita Sari A(2).

BACKGROUND: Drug-resistant tuberculosis (DR-TB) continues to be a global threat. Moxifloxacin is one of the components of the shorter treatment regimen which is suspected to increase the risk of QT prolongation, although it is also likely to be the most effective against DR-TB. A study to evaluate the correlation between the concentration of moxifloxacin and QTc interval in RR-TB patients who received shorter regimens is needed.
METHODS: This was an observational study in 2 groups of RR-TB patients on shorter treatment regimens (intensive phase and continuation phase), contain moxifloxacin with body weight-adjusted dose. Blood samples were collected at 2 h after taking the 48th-hour dose and 1 h before taking the 72nd-hour dose.
RESULTS: Forty-five RR-TB patients were included in this study. At 2 h after taking the 48th-hour dose, the mean of QTc interval in intensive phase and continuation phase was 444.38 ms vs. 467.94 ms, p = 0.026, while mean of moxifloxacin concentration in intensive phase and continuation phase was 4.3 μg/mL vs. 4.61 μg/mL, p = 0.686). At 1 h before taking the 72nd-hour dose, both moxifloxacin concentration and QTc interval in intensive phase and continuation showed no significant difference with p-value of 0.610 and 0.325, respectively. At 2 h after taking the 48th-dose, moxifloxacin concentration did not correlate with QTc interval, both in intensive phase (p = 0.576) and in continuation phase (p = 0.691). At 1 h before taking the 72nd-hour dose, moxifloxacin concentration also did not correlate with QTc interval in intensive phase (p = 0.531) and continuation phase (p = 0.209).

CONCLUSIONS: Our study found that moxifloxacin concentration did not correlate with QTc interval, which indicates the safe use of moxifloxacin on QTc interval. In addition to close monitoring of QTc interval, the clinicians should also consider other variables which potentially increase risk for QTc prolongation in DR-TB patients who received shorter treatment regimens.

DOI: 10.1016/j.jctube.2022.100320
PMCID: PMC9189108
PMID: 35706565

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

52. **Phylogenetic lineages of tuberculosis isolates and their association with patient demographics in Tanzania.**

BMC Genomics. 2022 Aug 5;23(1):561. doi: 10.1186/s12864-022-08791-3.

Mutayoba BK(1)(2), Michael Hoelscher(3), Heinrich N(3), Joloba ML(4)(5), Lyamuya E(6), Kilale AM(7), Range NS(7), Ngowi BJ(7)(8), Ntinginya NE(9), Mfaume SM(7), Wilfred A(7), Doulla B(10), Lyimo J(11), Kisonga R(11), Kingalu A(10), Kabahita JM(4), Guido O(4), Kabugo J(4), Adam I(4), Luutu M(5), Namaganda MM(5), Namutebi J(4), Kasule GW(4), Nakato H(4), Byabajungu H(4), Lutaaya P(4), Musisi K(4), Oola D(4), Mboowa G(12), Pletschette M(3).

BACKGROUND: Mycobacterium tuberculosis presents several lineages each with distinct characteristics of evolutionary status, transmissibility, drug resistance, host interaction, latency, and vaccine efficacy. Whole genome sequencing (WGS) has emerged as a new diagnostic tool to reliably inform the occurrence of phylogenetic lineages of Mycobacterium tuberculosis and examine their relationship with patient demographic characteristics and multidrug-resistance development.
METHODS: 191 Mycobacterium tuberculosis isolates obtained from a 2017/2018 Tanzanian drug resistance survey were sequenced on the Illumina Miseq platform at Supranational Tuberculosis Reference Laboratory in Uganda. Obtained fast-q files were imported into tools for resistance profiling and lineage inference (Kvarq v0.12.2, Mykrobe v0.8.1 and TBprofiler v3.0.5). Additionally for phylogenetic tree construction, RaxML-NG v1.0.3(25) was used to generate a maximum likelihood phylogeny with 800 bootstrap replicates. The resulting trees were plotted, annotated and visualized using ggtree v2.0.4 RESULTS: Most

[172(90.0%)] of the isolates were from newly treated Pulmonary TB patients. Coinfection with HIV was observed in 33(17.3%) TB patients. Of the 191 isolates, 22(11.5%) were resistant to one or more commonly used first line anti-TB drugs (FLD), 9(4.7%) isolates were MDR-TB while 3(1.6%) were resistant to all the drugs. Of the 24 isolates with any resistance conferring mutations, 13(54.2%) and 10(41.6%) had mutations in genes associated with resistance to INH and RIF respectively. The findings also show four major lineages i.e. Lineage 3[81 (42.4%)], followed by Lineage 4 [74 (38.7%)], the Lineage 1 [23 (12.0%)] and Lineages 2 [13 (6.8%)] circulaing in Tanzania.
CONCLUSION: The findings in this study show that Lineage 3 is the most prevalent lineage in Tanzania whereas drug resistant mutations were more frequent among isolates that belonged to Lineage 4.

DOI: 10.1186/s12864-022-08791-3
PMCID: PMC9356438
PMID: 35931954 [Indexed for MEDLINE]

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

53. **Failure or relapse predictors for the STREAM Stage 1 short regimen for RR-TB.**

Int J Tuberc Lung Dis. 2022 Aug 1;26(8):753-759. doi: 10.5588/ijtld.22.0073.

Kokebu DM(1), Ahmed S(2), Moodliar R(3), Chiang CY(4), Torrea G(5), Van Deun A(5), Goodall RL(2), Rusen ID(6), Meredith SK(2), Nunn AJ(2).
BACKGROUND: STREAM (Standardised Treatment Regimens of Anti-tuberculosis drugs for Multidrug-Resistant Tuberculosis) Stage 1 demonstrated non-inferior efficacy of a short regimen for rifampicin-resistant TB (RR-TB) compared to a long regimen as recommended by the WHO. The present paper analyses factors associated with a definite or probable failure or relapse (FoR) event in participants receiving the Short regimen.METHODS: This analysis is restricted to 253 participants allocated to the Short regimen and is based on the protocol-defined modified intention to treat (mITT) population. Multivariable Cox regression models were built using backwards elimination with an exit probability of P = 0.157, equivalent to the Akaike Information Criterion, to identify factors independently associated with a definite or probable FoR event.RESULTS: Four baseline factors were identified as being significantly associated with the risk of definite or probable FoR (male sex, a heavily positive baseline smear grade, HIV co-infection and the presence of costophrenic obliteration). There was evidence of association of culture positivity at Week 8 and FoR in a second

model and Week 16 smear positivity, presence of diabetes and of smoking in a third model.CONCLUSION: The factors associated with FoR outcomes identified in this analysis should be considered when determining the optimal shortened treatment regimen.

DOI: 10.5588/ijtld.22.0073
PMCID: PMC9341498
PMID: 35898125 [Indexed for MEDLINE]

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

54. **Travel reimbursements, distance to health facility and preventive treatment cascade for drug-resistant TB.**

Int J Tuberc Lung Dis. 2022 Aug 1;26(8):789-791. doi: 10.5588/ijtld.22.0204.

Malik AA(1), Siddique M(2), Chandir S(3), Jaswal M(4), Siddiqui S(4), Fuad J(4), Khan AJ(3), Amanullah F(4), Hussain H(3).

DOI: 10.5588/ijtld.22.0204
PMID: 35898142 [Indexed for MEDLINE]

55. **Novel rrs mutations in second-line injectable drug-resistant clinical isolates of Mycobacterium tuberculosis from the Punjab province of Pakistan.**

J Infect Chemother. 2022 Aug;28(8):1119-1124. doi: 10.1016/j.jiac.2022.03.027. Epub 2022 Apr 12.

Sarwer MI(1), Khan MT(2), Khurshid S(3).

INTRODUCTION: Phenotypic drug susceptibility testing is the most common approach to assess drug-resistant isolates; however, molecular methods of drug susceptibility testing are fast, accurate hence, offer less time for transmission during the diagnosis period. As data on the molecular methods regarding injectable drug resistance in the Punjab province of Pakistan is limited, therefore in this study, we aimed to analyze the mutations in the rrs gene behind second-line injectable drug resistance.
MATERIAL AND METHODS: Mycobacterium tuberculosis isolates were collected from the sputum of 5362 TB suspects. The strains confirmed for resistant to injectable drugs through drug susceptibility testing were further proceeded. The 1537bp rrs gene was amplified with the help of three sets of primers with overlapping regions and DNA sequencing was performed. Obtained sequences were

aligned with reference sequence to find mutations. RFLP-PCR method was also optimized for rapid detection of a common (143bp and 205bp) rrs gene mutation.
RESULTS: Among 172 rifampicin resistance isolates, 163(95%) were resistant to both rifampicin and isoniazid, and 9 (5%) were resistant to only rifampicin. Among the resistant samples, 12 (6.9%) samples were resistant to all three injectable drugs. Sixty out of 172 (34.9%) samples showed resistance to at least one drug and 10 (5.8%) samples were resistant to two drugs among the 3 s-line drugs. Sequencing analysis showed novel mutations in different samples at positions 443InsC, 19DelT, 29G>A, 48C>T, 50G>C, 265InsT, 423T>G, 476InsA, 446A>G, 563DelA, 695G>A, 805DelA, 900G>A, and 1510A>G, while some already reported mutations at position 1401A>G, 1402A>G, and 1484G>T were also observed. MIC of novel rrs gene mutations in KAN, CAP, and AMK resistant isolates were found between 2.5 mg/L-3.05 mg/L, 2.08 mg/L-3.0 mg/L, and 2.1 mg/L-2.7 mg/L respectively.
CONCLUSION: Novel mutations in the rrs gene reported in this study may confer second-line injectable drugs resistance in Mtb. This molecular insight into second-line injectable drug resistance is useful for better management of resistance Mtb in high burden countries.

DOI: 10.1016/j.jiac.2022.03.027
PMID: 35428575 [Indexed for MEDLINE]

56. **A CRISPR-guided mutagenic DNA polymerase strategy for the detection of antibiotic-resistant mutations in M. tuberculosis.**

Mol Ther Nucleic Acids. 2022 Jul 12;29:354-367. doi: 10.1016/j.omtn.2022.07.004. eCollection 2022 Sep 13.

Feng S(1)(2)(3), Liang L(1)(2)(3), Shen C(4)(5), Lin D(1)(2)(3), Li J(1)(2)(3), Lyu L(1)(2)(3), Liang W(1)(2)(3), Zhong LL(1)(2)(3), Cook GM(6)(7), Doi Y(8)(9), Chen C(4)(5), Tian GB(1)(2)(3)(10).

A sharp increase in multidrug-resistant tuberculosis (MDR-TB) threatens human health. Spontaneous mutation in essential gene confers an ability of Mycobacterium tuberculosis resistance to anti-TB drugs. However, conventional laboratory strategies for identification and prediction of the mutations in this slowly growing species remain challenging. Here, by combining XCas9 nickase and the error-prone DNA polymerase A from M. tuberculosis, we constructed a CRISPR-guided DNA polymerase system, CAMPER, for effective site-directed mutagenesis of drug-target genes in mycobacteria. CAMPER was able to generate

mutagenesis of all nucleotides at user-defined loci, and its bidirectional mutagenesis at nick sites allowed editing windows with lengths up to 80 nucleotides. Mutagenesis of drug-targeted genes in Mycobacterium smegmatis and M. tuberculosis with this system significantly increased the fraction of the antibiotic-resistant bacterial population to a level approximately 60- to 120-fold higher than that in unedited cells. Moreover, this strategy could facilitate the discovery of the mutation conferring antibiotic resistance and enable a rapid verification of the growth phenotype-mutation genotype association. Our data demonstrate that CAMPER facilitates targeted mutagenesis of genomic loci and thus may be useful for broad functions such as resistance prediction and development of novel TB therapies.

DOI: 10.1016/j.omtn.2022.07.004
PMCID: PMC9358013
PMID: 35950213

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

57. **Letter to the Editor: Isolation of Nontuberculous Mycobacteria During Multidrug-Resistant Tuberculosis Treatment: Colonization or Disease?**

Microb Drug Resist. 2022 Aug;28(8):906-908. doi: 10.1089/mdr.2022.0015. Epub 2022 Jul 29.

Zhang YL(1), Pan ZY(1), Chen J(2), Li BX(3), Duan QH(1), Li YH(1), Ruan HL(1), Gan H(4).

DOI: 10.1089/mdr.2022.0015
PMID: 35905051 [Indexed for MEDLINE]

58. **High proportion of tuberculosis transmission among social contacts in rural China: a 12-year prospective population-based genomic epidemiological study.**

Emerg Microbes Infect. 2022 Aug 11:1-40. doi: 10.1080/22221751.2022.2112912. Online ahead of print.

Li M(1)(2), Guo M(3), Peng Y(4), Jiang Q(1)(5), Xia L(6), Zhong S(7), Qiu Y(3), Su X(7), Zhang S(6), Yang C(1)(8), Mijiti P(1), Mao Q(1), Takiff H(9), Li F(4), Chen C(6), Gao Q(1)(2).

Tuberculosis (TB) is more prevalent in rural than urban areas in China, and delineating TB transmission patterns in rural populations could improve TB control. We conducted a prospective population-based study of culture-positive pulmonary TB patients diagnosed between July 1, 2009 and December 31, 2020 in two rural counties in China. Genomic clusters were defined with a threshold distance of 12-single-nucleotide-polymorphisms, based on whole-genome sequencing. Risk factors for clustering were identified by logistic regression. Transmission links were sought through epidemiological investigation of genomic-clustered patients. Of 1517 and 751 culture-positive pulmonary TB patients in Wusheng and Wuchang counties, respectively, 1289 and 699 strains were sequenced. Overall, 624 (31.4%, 624/1988) patients were grouped into 225 genomic clusters. Epidemiological links were confirmed in 41.8% (196/469) of clustered isolates, including family (32.7%, 64/196) and social contacts (67.3%, 132/196). Social contacts were generally with relatives, within the community or in shared aggregated settings outside the community, but the proportion of clustered contacts in each category differed between the two sites. The time interval between diagnosis of student cases and contacts was significantly shorter than family and social contacts, probably due to enhanced student contact screening. Transmission of multidrug-resistant (MDR) strains was likely responsible for 81.4% (83/102) of MDR-TB cases, with minimal acquisition of additional resistance mutations. A large proportion of TB transmission in rural China occurred among social contacts, suggesting that active screening and aggressive contact tracing could benefit TB control, but contact screening should be tailored to local patterns of social interactions.

DOI: 10.1080/22221751.2022.2112912
PMID: 35950916

59. **Structure-Activity Relationship of Penem Antibiotic Side Chains Used against Mycobacteria Reveals Highly Active Compounds.**

ACS Infect Dis. 2022 Aug 12;8(8):1627-1636. doi: 10.1021/acsinfecdis.2c00229. Epub 2022 Aug 2.

Batchelder HR(1), Zandi TA(2), Kaushik A(3), Naik A(1), Story-Roller E(3), Maggioncalda EC(3), Lamichhane G(3), Nuermberger EL(3), Townsend CA(1).

The rise of antibiotic-resistant Mycobacterium tuberculosis and non-tuberculous mycobacterial infections has placed ever-increasing importance on discovering new antibiotics to treat these diseases. Recently, a new penem, T405, was discovered to have strong antimicrobial activity against M. tuberculosis and Mycobacteroides abscessus. Here, a penem library of C2 side-chain variants was synthesized, and their antimicrobial activities were evaluated against M.

tuberculosis H37Rv and M. abscessus ATCC 19977. Several new penems with antimicrobial activity stronger than the standard-of-care carbapenem antibiotics were identified with some candidates improving on the activity of the lead compound, T405. Moreover, many candidates showed little or no increase in the minimum inhibitory concentration in the presence of serum compared to the highly protein-bound T405. The penems with the strongest activity identified in this study were then biochemically characterized by reaction with the representative l,d-transpeptidase LdtMt2 and the representative penicillin-binding protein d,d-carboxypeptidase DacB2.

DOI: 10.1021/acsinfecdis.2c00229
PMID: 35916356 [Indexed for MEDLINE]

60. **Phosphatidylcholine (18:0/20:4), a potential biomarker to predict ethionamide-induced hepatic steatosis in rats.**

J Appl Toxicol. 2022 Sep;42(9):1533-1547. doi: 10.1002/jat.4324. Epub 2022 Mar 29.

Muta K(1), Saito K(2), Kemmochi Y(1), Masuyama T(1), Kobayashi A(1), Saito Y(2), Sugai S(1).

Ethionamide (ETH), a second-line drug for multidrug-resistant tuberculosis, is known to cause hepatic steatosis in rats and humans. To investigate predictive biomarkers for ETH-induced steatosis, we performed lipidomics analysis using plasma and liver samples collected from rats treated orally with ETH at 30 and 100 mg/kg for 14 days. The ETH-treated rats developed hepatic steatosis with Oil Red O staining-positive vacuolation in the centrilobular hepatocytes accompanied by increased hepatic contents of triglycerides (TG) and decreased plasma TG and total cholesterol levels. A multivariate analysis for lipid profiles revealed differences in each of the 35 lipid species in the plasma and liver between the control and the ETH-treated rats. Of those lipids, phosphatidylcholine (PC) (18:0/20:4) decreased dose-dependently in both the plasma and liver. Moreover, serum TG-rich very low-density lipoprotein (VLDL) levels, especially the large particle fraction of VLDL composed of PC containing arachidonic acid (20:4) involved in hepatic secretion of TG, were decreased dose-dependently. In conclusion, the decreased PC (18:0/20:4) in the liver, possibly leading to suppression of hepatic TG secretion, was considered to be involved in the pathogenesis of the ETH-induced hepatic steatosis. Therefore, plasma PC (18:0/20:4) levels are proposed as mechanism-related biomarkers for ETH-induced hepatic steatosis.

Ltd.

DOI: 10.1002/jat.4324
PMID: 35315511 [Indexed for MEDLINE]

61. **Proteomic analysis of sequential isolates of multidrug-resistant Mycobacterium tuberculosis during treatment failure: Altered protein expression in failed MDR-TB treatment.**

J Infect. 2022 Aug 17:S0163-4453(22)00473-X. doi: 10.1016/j.jinf.2022.08.010. Online ahead of print.

Lee DG(1), Kim HJ(2), Park MJ(3), Hong JH(2), Ryoo S(4).

DOI: 10.1016/j.jinf.2022.08.010
PMID: 35987390

Conflict of interest statement: Declaration of interests none.

63. **Evaluation of the use of GeneXpert MTB/RIF in a zone with high burden of tuberculosis in Thailand.**

PLoS One. 2022 Jul 27;17(7):e0271130. doi: 10.1371/journal.pone.0271130. eCollection 2022.

Pongpeeradech N(1), Kasetchareo Y(2)(3), Chuchottaworn C(4), Lawpoolsri S(1)(5), Silachamroon U(6), Kaewkungwal J(1)(5).

GeneXpert MTB/RIF is a reliable molecular diagnostic tool capable of detecting Mycobacterium tuberculosis (MTB) and identifying genetic determinants of rifampicin (RIF) resistance. This study aimed to assess physicians' diagnostic decision-making processes for TB based on GeneXpert MTB/RIF results and how this affected the initiation of multidrug resistance (MDR) treatment. This study employed a mixed method: data were collected retrospectively from the medical records of TB patients and in-depth interviews were conducted with healthcare workers in areas with a high TB burden in Thailand. A total of 2,030 complete TB records from 2 patient groups were reviewed, including 1443 suspected cases with negative smear results and 587 with high risk of MDR-TB. GeneXpert MTB/RIF was routinely used to assist the physicians in their decision-making for the diagnosis of pulmonary tuberculosis (PTB) and the initiation of MDR-TB treatment. The physicians used it as a "rule-in test" for all patients with negative chest X-rays (CXR) and smear results, to ensure timely treatment.

Approximately one-fourth of the patients with negative CXR/smear and GeneXpert MTB/RIF results were diagnosed with PTB by the physicians, who based their decisions on other evidence, such as clinical symptoms, and did not use GeneXpert MTB/RIF as a "rule-out test." GeneXpert MTB/RIF proved effective in early detection within a day, thereby radically shortening the time required to initiate second-line drug treatment. Despite its high sensitivity for detecting PTB and MDR-TB, GeneXpert MTB/RIF had contradictory results (false positive and/or false negative) for 21.8% of cases among patients with negative smear results and 41.1% of cases among patients with high risk of MDR-TB. Therefore, physicians still used the results of other conventional tests in their decision-making process. It is recommended that GeneXpert MTB/RIF should be established at all points of care and be used as the initial test for PTB and MDR-TB diagnosis.

DOI: 10.1371/journal.pone.0271130
PMCID: PMC9328536
PMID: 35895742 [Indexed for MEDLINE]

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

64. **Tuberculosis Treatment Outcomes of Patients with Diabetes Mellitus.**

Isr Med Assoc J. 2022 Aug;24(8):503-508.

Tzanani I(1), Bendayan D(1)(2), Jaffe A(3), Mor Z(1)(4)(5).

BACKGROUND: Diabetes mellitus (DM) is one of the risk factors for progression from latent to active tuberculosis. However, the effect of DM on subsequent tuberculosis treatment is still inconclusive.
OBJECTIVES: To compare tuberculosis treatment outcomes and the rate of drug resistance of tuberculosis patients with or without DM.
METHODS: This case-control study was conducted between 2005 and 2015 at the only tuberculosis ward in Israel. All 80 tuberculosis patients who had DM and were hospitalized during the study period were included in this study, as were a randomized sample of 213 tuberculosis patients without DM. Demographic, clinical, and laboratory data were collected from patient files in the hospital and clinics after discharge.
RESULTS: Tuberculosis patients with DM were more often older and more likely to be Israeli citizens with a lower socioeconomic status than patients without DM. No statistically significant differences were found in clinical presentation, radiological findings, and sputum smear tests between the two groups. Culture converting times were prolonged in patients with DM compared to normoglycemic

patients. Multidrug drug resistance tuberculosis was more common among normoglycemic tuberculosis patients than tuberculosis patients with DM (9.2% vs. 1.6%, P = 0.12). Treatment success rates were 76.2% and 83.1% for tuberculosis patients with or without DM, respectively (P = 0.18). DM was not statistically significant in the multivariate analysis predicting treatment success, which controlled for age, citizenship, compliance, addictions, and chronic diseases. CONCLUSIONS: The presence of DM does not necessarily affect tuberculosis treatment outcomes as long as treatment compliance is optimal.

PMID: 35972007 [Indexed for MEDLINE]

65. **Diagnostic capacities for multidrug-resistant tuberculosis in the WHO European Region - action is needed by all Member States.**

J Mol Diagn. 2022 Aug 11:S1525-1578(22)00219-7. doi: 10.1016/j.jmoldx.2022.07.005. Online ahead of print.

Maurer FP(1), Shubladze N(2), Kalmambetova G(3), Felker I(4), Kuchukhidze G(5), Köser CU(6), Cirillo DM(7), Drobniewski F(8), Yedilbayev A(5), Ehsani S(9); European Laboratory Initiative on TB, HIV and Viral Hepatitis(3).

The World Health Organization (WHO) recently revised its guidelines for rapid diagnosis of drug-resistant tuberculosis (DR-TB). This study aimed to investigate if tuberculosis reference diagnostic services are prepared to support these revisions. An online survey was performed among 44 TB National Reference Laboratories (NRL) in the WHO European Region. Questions addressed the use of WHO-recommended molecular techniques for the diagnosis of DR-TB, the techniques applied to investigate antimicrobial resistance, and questions on quality assurance. Among 35/44 (80%) participating NRL, 29/35 (83%) reported using the Cepheid GeneXpert platform as the initial test to detect Mycobacterium tuberculosis complex (MTBC) and rifampicin (RMP) resistance. Five laboratories reported using another WHO-recommended, moderate complexity automated nucleic acid amplification test for detection of MTBC and resistance to RMP and INH. Most (32/35, 91%) NRL reported capacity to test second-line drugs that have been in clinical use for many years (fluoroquinolones, linezolid, and injectable agents). Only 23/35 (66%) and 21/35 (60%) NRL reported capacity to test bedaquiline and clofazimine. Further efforts will be needed to improve the availability of quality-controlled testing against WHO Group A and Group B drugs. Earlier considerations on the scale-up of diagnostic capacities should be enforced as part of future approval processes for new antimycobacterial agents.

DOI: 10.1016/j.jmoldx.2022.07.005
PMID: 35964846

66. **Pharmacogenetics of Between-Individual Variability in Plasma Clearance of Bedaquiline and Clofazimine in South Africa.**

J Infect Dis. 2022 Aug 12;226(1):147-156. doi: 10.1093/infdis/jiac024.

Haas DW(1)(2), Abdelwahab MT(3), van Beek SW(4), Baker P(5), Maartens G(3), Bradford Y(6), Ritchie MD(7), Wasserman S(8), Meintjes G(9)(10), Beeri K(5), Gandhi NR(11)(12), Svensson EM(4)(13), Denti P(3), Brust JCM(14).

BACKGROUND: Plasma bedaquiline clearance is reportedly more rapid with African ancestry. Our objective was to determine whether genetic polymorphisms explained between-individual variability in plasma clearance of bedaquiline, its M2 metabolite, and clofazimine in a cohort of patients treated for drug-resistant tuberculosis in South Africa.
METHODS: Plasma clearance was estimated with nonlinear mixed-effects modeling. Associations between pharmacogenetic polymorphisms, genome-wide polymorphisms, and variability in clearance were examined using linear regression models.
RESULTS: Of 195 cohort participants, 140 were evaluable for genetic associations. Among 21 polymorphisms selected based on prior genome-wide significant associations with any drug, rs776746 (CYP3A5∗3) was associated with slower clearance of bedaquiline (P = .0017) but not M2 (P = .25). CYP3A5∗3 heterozygosity and homozygosity were associated with 15% and 30% slower bedaquiline clearance, respectively. The lowest P value for clofazimine clearance was with VKORC1 rs9923231 (P = .13). In genome-wide analyses, the lowest P values for clearance of bedaquiline and clofazimine were with RFX4 rs76345012 (P = 6.4 × 10-7) and CNTN5 rs75285763 (P = 2.9 × 10-8), respectively.
CONCLUSIONS: Among South Africans treated for drug-resistant tuberculosis, CYP3A5∗3 was associated with slower bedaquiline clearance. Different CYP3A5∗3 frequencies among populations may help explain the more rapid bedaquiline clearance reported in Africans. Associations with RFX4 and CNTN5 are likely by chance alone.

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PMCID: PMC9373148
PMID: 35091749 [Indexed for MEDLINE]

Conflict of interest statement: Potential conflicts of interest. All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

67. **A case of primary multidrug-resistant pulmonary tuberculosis with high minimum inhibitory concentration value for bedaquiline.**

J Infect Chemother. 2022 Aug;28(8):1193-1197. doi: 10.1016/j.jiac.2022.04.028. Epub 2022 May 10.

Kobayashi M(1), Motoki Y(2), Yamagishi T(3), Hirano H(3), Nonaka M(3), Aono A(4), Mitarai S(4), Saito T(3).

Bedaquiline is a new ATP synthesis inhibitor developed as an anti-tuberculosis agent. It has resistance-associated variants (RAV), regardless of preceding bedaquiline exposure. Herein, we describe the case of a patient with multidrug-resistant tuberculosis (MDR-TB) who had no history of bedaquiline therapy but presented a relatively high minimum inhibitory concentration (MIC) of bedaquiline (1 μg/mL). Whole genome sequencing revealed a mutation in the resistance-associated gene Rv0678. The patient was first treated with a five-drug regimen (bedaquiline, delamanid, levofloxacin, cycloserine, and amikacin), which induced negative sputum culture conversion. Despite the successful treatment outcome, several questions remain regarding the efficacy of bedaquiline in this patient. Bedaquiline is an indispensable drug for MDR-TB treatment, but its clinical efficiency in the presence of Rv0678 mutations remains unclear. Therefore, evaluating the MIC of bedaquiline even in patients without a history of bedaquiline use is important for therapeutic regimen selection and may emphasize the importance of therapeutic drug monitoring in cases of bedaquiline RAV.

DOI: 10.1016/j.jiac.2022.04.028
PMID: 35550867 [Indexed for MEDLINE]

68. **Lysocin E Targeting Menaquinone in the Membrane of Mycobacterium tuberculosis Is a Promising Lead Compound for Antituberculosis Drugs.**

Antimicrob Agents Chemother. 2022 Aug 15:e0017122. doi: 10.1128/aac.00171-22. Online ahead of print.

Geberetsadik G(1)(2), Inaizumi A(1), Nishiyama A(1), Yamaguchi T(1)(3), Hamamoto H(4), Panthee S(5)(6), Tamaru A(7), Hayatsu M(8), Mizutani Y(8)(9), Kaboso SA(1), Hakamata M(1)(10), Ilinov A(1)(11), Ozeki Y(1), Tateishi Y(1), Sekimizu K(5), Matsumoto S(1)(12).

Tuberculosis remains a public health crisis and a health security threat. There is an urgent need to develop new antituberculosis drugs with novel modes of action to cure drug-resistant tuberculosis and shorten the chemotherapy period by sterilizing tissues infected with dormant bacteria. Lysocin E is an antibiotic that showed antibacterial activity against Staphylococcus aureus by binding to its menaquinone (commonly known as vitamin K2). Unlike S. aureus, menaquinone is essential in both growing and dormant Mycobacterium tuberculosis. This study aims to evaluate the antituberculosis activities of lysocin E and decipher its mode of action. We show that lysocin E has high in vitro activity against both drug-susceptible and drug-resistant Mycobacterium tuberculosis var. tuberculosis and dormant mycobacteria. Lysocin E is likely bound to menaquinone, causing M. tuberculosis membrane disruption, inhibition of oxygen consumption, and ATP synthesis. Thus, we have concluded that the high antituberculosis activity of lysocin E is attributable to its synergistic effects of membrane disruption and respiratory inhibition. The efficacy of lysocin E against intracellular M. tuberculosis in macrophages was lower than its potent activity against M. tuberculosis in culture medium, probably due to its low ability to penetrate cells, but its efficacy in mice was still superior to that of streptomycin. Our findings indicate that lysocin E is a promising lead compound for the development of a new tuberculosis drug that cures drug-resistant and latent tuberculosis in a shorter period.

DOI: 10.1128/aac.00171-22
PMID: 35969044

69. **A data compendium associating the genomes of 12,289 Mycobacterium tuberculosis isolates with quantitative resistance phenotypes to 13 antibiotics.**

PLoS Biol. 2022 Aug 9;20(8):e3001721. doi: 10.1371/journal.pbio.3001721. eCollection 2022 Aug.

The CRyPTIC Consortium.

Comment in
Genome-wide association studies of global Mycobacterium tuberculosis resistance to thirteen antimicrobials in 10,228 genomes identify new resistance mechanisms.

The Comprehensive Resistance Prediction for Tuberculosis: an International Consortium (CRyPTIC) presents here a data compendium of 12,289 Mycobacterium tuberculosis global clinical isolates, all of which have undergone whole-genome sequencing and have had their minimum inhibitory concentrations to 13 antitubercular drugs measured in a single assay. It is the largest matched phenotypic and genotypic dataset for M. tuberculosis to date. Here, we provide a summary detailing the breadth of data collected, along with a description of how the isolates were selected, collected, and uniformly processed in CRyPTIC partner laboratories across 23 countries. The compendium contains 6,814 isolates resistant to at least 1 drug, including 2,129 samples that fully satisfy the clinical definitions of rifampicin resistant (RR), multidrug resistant (MDR), pre-extensively drug resistant (pre-XDR), or extensively drug resistant (XDR). The data are enriched for rare resistance-associated variants, and the current limits of genotypic prediction of resistance status (sensitive/resistant) are presented by using a genetic mutation catalogue, along with the presence of suspected resistance-conferring mutations for isolates resistant to the newly introduced drugs bedaquiline, clofazimine, delamanid, and linezolid. Finally, a case study of rifampicin monoresistance demonstrates how this compendium could be used to advance our genetic understanding of rare resistance phenotypes. The data compendium is fully open source and it is hoped that it will facilitate and inspire future research for years to come.

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PMCID: PMC9363010
PMID: 35944069 [Indexed for MEDLINE]

Conflict of interest statement: I have read the journal's policy and the authors of this manuscript have the following competing interests: E.R. is employed by Public Health England and holds an honorary contract with Imperial College London. I.F.L. is Director of the Scottish Mycobacteria Reference Laboratory. S.N. receives funding from German Center for Infection Research, Excellenz Cluster Precision Medicine in Chronic Inflammation, Leibniz Science Campus Evolutionary Medicine of the LUNG (EvoLUNG)tion EXC 2167. P.S. is a consultant at Genoscreen. T.R. is funded by NIH and DoD and receives salary support from the non-profit organization FIND. T.R. is a co-founder, board member and shareholder of Verus Diagnostics Inc, a company that was founded with the intent of developing diagnostic assays. Verus Diagnostics was not involved in any way with data collection, analysis or publication of the results. T.R. has not received any financial support from Verus Diagnostics. UCSD Conflict of Interest office has reviewed and approved T.R.'s role in Verus Diagnostics Inc. T.R. is a co-inventor of a provisional patent for a TB diagnostic assay (provisional patent #: 63/048.989). T.R. is a co-inventor on a patent associated with the processing of TB sequencing data (European Patent Application No. 14840432.0 &

USSN 14/912,918). T.R. has agreed to “donate all present and future interest in and rights to royalties from this patent” to UCSD to ensure that he does not receive any financial benefits from this patent. S.S. is working and holding ESOPs at HaystackAnalytics Pvt. Ltd. (Product: Using whole genome sequencing for drug susceptibility testing for Mycobacterium tuberculosis). G.F.G. is listed as an inventor on patent applications for RBD-dimer-based CoV vaccines. The patents for RBD-dimers as protein subunit vaccines for SARS-CoV-2 have been licensed to Anhui Zhifei Longcom Biopharmaceutical Co. Ltd, China.

70. **Strengthening resistance testing for tuberculosis in India - Investment cost, throughput, and efficiency of new laboratories.**

Tuberculosis (Edinb). 2022 Aug 6;136:102245. doi: 10.1016/j.tube.2022.102245. Online ahead of print.

Bashir S(1), Sarin S(2), Chadha SS(2), Kalra A(2), ThekkePurakkal AS(2), Duraisamy K(2), Saacks S(3), Gwaza GP(3), Ongarello S(3), Denkinger CM(4).

A lack of laboratory capacity for drug-resistant tuberculosis (DR-TB) testing is a major barrier to DR-TB control. To overcome this barrier, the Central Tuberculosis Division (CTD), Ministry of Health and Family Welfare (MoHFW), Government of India (GoI), and FIND India established a partnership under the National Tuberculosis Elimination Program (NTEP) to strengthen and expand tuberculosis (TB) laboratory diagnostic capabilities. This partnership has led to the establishment of 61 culture & DST laboratories, increasing the testing capacity to a capability of performing over 200,000 liquid cultures and over 170,000 molecular drug sensitivity tests annually. In this study, we assess the data on throughput, efficiency, investment cost, and the capacity of the laboratory services supported by this partnership to understand impact and inform future resource allocation. We estimated the technical efficiency using Stochastic Frontier Analysis (SFA). Our results show that the established laboratory network is operating at 69% efficiency, with the capacity to perform an additional 450,000 cultures and 180,000 first-line molecular drug-susceptibility tests by 2025. This additional capacity, together with current efforts to enhance the laboratory network, has the potential to make a significant contribution to NTEP's TB elimination target by 2025.

DOI: 10.1016/j.tube.2022.102245
PMID: 35961095

71. **Minimum inhibitory concentration of cycloserine against Mycobacterium tuberculosis using the MGIT 960 system and a proposed critical concentration.**

Int J Infect Dis. 2022 Aug;121:148-151. doi: 10.1016/j.ijid.2022.05.030. Epub 2022 May 13.

Wu X(1), Shang Y(1), Ren W(1), Wang W(1), Wang Y(2), Xue Z(1), Li S(3), Pang Y(4).

OBJECTIVES: We aimed to determine the breakpoint of cycloserine (CS) susceptibility in MGIT and to describe the molecular characteristics of CS-resistant Mycobacterium tuberculosis (MTB) isolates.
METHODS: A total of 124 MTB isolates were recruited in our analysis. Minimum inhibitory concentration (MIC) was determined using the MGIT system. The mutations of MTB isolates within alr, ddl, ald, and cycA, potentially conferring CS resistance were analyzed by the whole-genome sequencing.
RESULTS: In vitro drug susceptibility testing of isolates with doubling concentrations of CS revealed that the modal MIC values was 4 mg/L for MGIT, accounting for 35.5% (44/124) of isolates tested. Seven isolates harbored mutations conferring CS resistance, consisting of five with alr mutations and two with ald mutations. On the basis of the MIC distributions of wild-type and resistotype populations, we proposed a tentative epidemiologic cut-off value of 16 mg/l. The proportion of CS resistance in extensively drug-resistant TB was significantly higher than that of multidrug-resistant TB.
CONCLUSION: In conclusion, we propose critical concentration for MGIT 960 to properly diagnose CS-resistant MTB and demonstrate that mutations in alr and ald genes are the major mechanism conferring CS resistance in clinical isolates.

DOI: 10.1016/j.ijid.2022.05.030
PMID: 35577251 [Indexed for MEDLINE]

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

72. **Modification of bacterial cell membrane dynamics and morphology upon exposure to sub inhibitory concentrations of ciprofloxacin.**

Biochim Biophys Acta Biomembr. 2022 Aug 1;1864(8):183935. doi: 10.1016/j.bbamem.2022.183935. Epub 2022 Apr 21.

Ponmalar II(1), Swain J(2), Basu JK(3).

Ciprofloxacin (CPX), a second generation fluoroquinolone antibiotic, is used as a primary antibiotic for treatment against gastroenteritis, drug-resistant tuberculosis, and malignant otitis externa. CPX is a broad spectrum antibiotic that targets the DNA gyrase of both Gram-positive and Gram-negative bacteria. Irrational and improper usage of CPX results in emergence of CPX resistant organisms emphasizing the importance of using lethal doses of CPX. Here, we have systematically analysed the effect of CPX at sub lethal concentrations on live E. coli membrane and growth dynamics. As a result of CPX interaction at sub-lethal concentrations, we detected filamentation of the bacterial cells during cell division. Although CPX is a DNA targeting antibiotic and did not result in considerable increase of live E. coli cell surface roughness, we observed significant enhancement in the lipid diffusion coefficients possibly due to disrupted lipid packing or altered lipid composition. Interestingly, we seem to observe slightly higher extent of lipid diffusion alteration when bacterial inner membrane specific label FM4-64 was used in comparison to the non-specific membrane dye. Both these results are contrary to that observed in bacterial cells for colistin, a membrane targeting antibiotics. Our work highlights the need for using multiple, complementary surface and depth sensitive techniques to obtain information on the realistic nature of bacterial cell membrane remodelling due to non-membrane targeting antibiotics. Our work could have implications for identification of potential biomembrane markers at sub-lethal concentrations even for antibiotics which are non-membrane targeting that could help in unravelling pathways for emergence of antimicrobial resistance.

DOI: 10.1016/j.bbamem.2022.183935
PMID: 35461827 [Indexed for MEDLINE]

73. **Genome-wide association studies of global Mycobacterium tuberculosis resistance to 13 antimicrobials in 10,228 genomes identify new resistance mechanisms.**

PLoS Biol. 2022 Aug 9;20(8):e3001755. doi: 10.1371/journal.pbio.3001755. eCollection 2022 Aug.

The CRyPTIC Consortium.

Comment in
A data compendium associating the genomes of 12,289 Mycobacterium tuberculosis isolates with quantitative resistance phenotypes to 13 antibiotics.

The emergence of drug-resistant tuberculosis is a major global public health concern that threatens the ability to control the disease. Whole-genome sequencing as a tool to rapidly diagnose resistant infections can transform patient treatment and clinical practice. While resistance mechanisms are well understood for some drugs, there are likely many mechanisms yet to be uncovered, particularly for new and repurposed drugs. We sequenced 10,228 Mycobacterium tuberculosis (MTB) isolates worldwide and determined the minimum inhibitory concentration (MIC) on a grid of 2-fold concentration dilutions for 13 antimicrobials using quantitative microtiter plate assays. We performed oligopeptide- and oligonucleotide-based genome-wide association studies using linear mixed models to discover resistance-conferring mechanisms not currently catalogued. Use of MIC over binary resistance phenotypes increased sample heritability for the new and repurposed drugs by 26% to 37%, increasing our ability to detect novel associations. For all drugs, we discovered uncatalogued variants associated with MIC, including in the Rv1218c promoter binding site of the transcriptional repressor Rv1219c (isoniazid), upstream of the vapBC20 operon that cleaves 23S rRNA (linezolid) and in the region encoding an α-helix lining the active site of Cyp142 (clofazimine, all $p < 10\text{-}7.7$). We observed that artefactual signals of cross-resistance could be unravelled based on the relative effect size on MIC. Our study demonstrates the ability of very large-scale studies to substantially improve our knowledge of genetic variants associated with antimicrobial resistance in M. tuberculosis.

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PMCID: PMC9363015
PMID: 35944070 [Indexed for MEDLINE]

Conflict of interest statement: I have read the journal's policy and the authors of this manuscript have the following competing interests: E.R. is employed by Public Health England and holds an honorary contract with Imperial College London. I.F.L. is Director of the Scottish Mycobacteria Reference Laboratory. S.N. receives funding from German Center for Infection Research, Excellenz Cluster Precision Medicine in Chronic Inflammation, Leibniz Science Campus Evolutionary Medicine of the LUNG (EvoLUNG)tion EXC 2167. P.S. is a consultant at Genoscreen. T.R. is funded by NIH and DoD and receives salary support from the non-profit organization FIND. T.R. is a co-founder, board member and shareholder of Verus Diagnostics Inc, a company that was founded with the intent of developing diagnostic assays. Verus Diagnostics was not involved in any way with data collection, analysis or publication of the results. T.R. has not received any financial support from Verus Diagnostics. UCSD Conflict of Interest office has reviewed and approved T.R.'s role in Verus Diagnostics Inc. T.R. is a co-inventor of a provisional patent for a TB diagnostic assay (provisional patent #: 63/048.989). T.R. is a co-inventor on a patent associated with the processing of TB sequencing data (European Patent Application No. 14840432.0 &

USSN 14/912,918). T.R. has agreed to “donate all present and future interest in and rights to royalties from this patent” to UCSD to ensure that he does not receive any financial benefits from this patent. S.S. is working and holding ESOPs at HaystackAnalytics Pvt. Ltd. (Product: Using whole genome sequencing for drug susceptibility testing for Mycobacterium tuberculosis). G.F.G. is listed as an inventor on patent applications for RBD-dimer-based CoV vaccines. The patents for RBD-dimers as protein subunit vaccines for SARS-CoV-2 have been licensed to Anhui Zhifei Longcom Biopharmaceutical Co. Ltd, China.

75. **Modulation of the Specificity of Carbapenems and Diazabicyclooctanes for Selective Activity against Mycobacterium tuberculosis.**

Antimicrob Agents Chemother. 2022 Aug 9:e0235721. doi: 10.1128/aac.02357-21. Online ahead of print.

Barnier JP(1)(2)(3), Saidjalolov S(4), Bouchet F(4), Mayer L(1), Edoo Z(1), Sayah I(1), Iannazzo L(4), Ethève-Quelquejeu M(4), Mainardi JL(1)(2)(3), Braud E(4), Arthur M(1).

Treatment of multidrug-resistant tuberculosis with combinations of carbapenems and β-lactamase inhibitors carries risks for dysbiosis and for the development of resistances in the intestinal microbiota. Using Escherichia coli producing carbapenemase KPC-2 as a model, we show that carbapenems can be modified to obtain drugs that are inactive against E. coli but retain antitubercular activity. Furthermore, functionalization of the diazabicyclooctanes scaffold provided drugs that did not effectively inactivate KPC-2 but retained activity against Mycobacterium tuberculosis targets.

DOI: 10.1128/aac.02357-21
PMID: 35943263

76. **Investigating resistance in clinical Mycobacterium tuberculosis complex isolates with genomic and phenotypic antimicrobial susceptibility testing: a multicentre observational study.**

Lancet Microbe. 2022 Jul 27:S2666-5247(22)00116-1. doi: 10.1016/S2666-5247(22)00116-1. Online ahead of print.

Finci I(1), Albertini A(2), Merker M(3), Andres S(4), Bablishvili N(5), Barilar I(6), Cáceres T(7), Crudu V(8), Gotuzzo E(7), Hapeela N(9), Hoffmann H(10), Hoogland C(2), Kohl TA(6), Kranzer K(11), Mantsoki A(2), Maurer FP(12), Nicol MP(13), Noroc E(8), Plesnik S(14), Rodwell T(15), Ruhwald M(2), Savidge T(16),

Salfinger M(17), Streicher E(18), Tukvadze N(5), Warren R(18), Zemanay W(9), Zurek A(19), Niemann S(6), Denkinger CM(20).

BACKGROUND: Whole-genome sequencing (WGS) of Mycobacterium tuberculosis complex has become an important tool in diagnosis and management of drug-resistant tuberculosis. However, data correlating resistance genotype with quantitative phenotypic antimicrobial susceptibility testing (AST) are scarce.
METHODS: In a prospective multicentre observational study, 900 clinical M tuberculosis complex isolates were collected from adults with drug-resistant tuberculosis in five high-endemic tuberculosis settings around the world (Georgia, Moldova, Peru, South Africa, and Viet Nam) between Dec 5, 2014, and Dec 12, 2017. Minimum inhibitory concentrations (MICs) and resulting binary phenotypic AST results for up to nine antituberculosis drugs were determined and correlated with resistance-conferring mutations identified by WGS.
FINDINGS: Considering WHO-endorsed critical concentrations as reference, WGS had high accuracy for prediction of resistance to isoniazid (sensitivity 98·8% [95% CI 98·5-99·0]; specificity 96·6% [95% CI 95·2-97·9]), levofloxacin (sensitivity 94·8% [93·3-97·6]; specificity 97·1% [96·7-97·6]), kanamycin (sensitivity 96·1% [95·4-96·8]; specificity 95·0% [94·4-95·7]), amikacin (sensitivity 97·2% [96·4-98·1]; specificity 98·6% [98·3-98·9]), and capreomycin (sensitivity 93·1% [90·0-96·3]; specificity 98·3% [98·0-98·7]). For rifampicin, pyrazinamide, and ethambutol, the specificity of resistance prediction was suboptimal (64·0% [61·0-67·1], 83·8% [81·0-86·5], and 40·1% [37·4-42·9], respectively). Specificity for rifampicin increased to 83·9% when borderline mutations with MICs overlapping with the critical concentration were excluded. Consequently, we highlighted mutations in M tuberculosis complex isolates that are often falsely identified as susceptible by phenotypic AST, and we identified potential novel resistance-conferring mutations.
INTERPRETATION: The combined analysis of mutations and quantitative phenotypes shows the potential of WGS to produce a refined interpretation of resistance, which is needed for individualised therapy, and eventually could allow differential drug dosing. However, variability of MIC data for some M tuberculosis complex isolates carrying identical mutations also reveals limitations of our understanding of the genotype and phenotype relationships (eg, including epistasis and strain genetic background).
FUNDING: Bill & Melinda Gates Foundation, German Centre for Infection Research, German Research Foundation, Excellence Cluster Precision Medicine of Inflammation (EXC 2167), and Leibniz ScienceCampus EvoLUNG.

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PMID: 35907429

Conflict of interest statement: Declaration of interests MM and SN report grants from the German Center for Infection Research, Excellenz Cluster Precision Medicine in Chronic Inflammation, and Leibniz Science Campus Evolutionary Medicine of the LUNG (EvoLUNG). TR reports personal fees from FIND, grants from the US National Institute of Allergy and Infectious Diseases, and is a board member for Verus Diagnostics; and has a provisional patent (#63/048.989) and a pending patent (#14840432.0) for tuberculosis diagnostics. All other authors declare no competing interests.

77. **Cryo-EM structure of Mycobacterium tuberculosis 50S ribosomal subunit bound with clarithromycin reveals dynamic and specific interactions with macrolides.**

Emerg Microbes Infect. 2022 Dec;11(1):293-305. doi: 10.1080/22221751.2021.2022439.

Zhang W(1)(2), Li Z(3)(4), Sun Y(5), Cui P(6), Liang J(7), Xing Q(1), Wu J(6), Xu Y(1), Zhang W(6), Zhang Y(6)(8), He L(1)(9), Gao N(3).

Tuberculosis (TB) is the leading infectious disease caused by Mycobacterium tuberculosis (Mtb). Clarithromycin (CTY), an analog of erythromycin (ERY), is more potent against multidrug-resistance (MDR) TB. ERY and CTY were previously reported to bind to the nascent polypeptide exit tunnel (NPET) near peptidyl transferase center (PTC), but the only available CTY structure in complex with D. radiodurans (Dra) ribosome could be misinterpreted due to resolution limitation. To date, the mechanism of specificity and efficacy of CTY for Mtb remains elusive since the Mtb ribosome-CTY complex structure is still unknown. Here, we employed new sample preparation methods and solved the Mtb ribosome-CTY complex structure at 3.3Å with cryo-EM technique, where the crucial gate site A2062 (E. coli numbering) is located at the CTY binding site within NPET. Two alternative conformations of A2062, a novel syn-conformation as well as a swayed conformation bound with water molecule at interface, may play a role in coordinating the binding of specific drug molecules. The previously overlooked C-H hydrogen bond (H-bond) and π interaction may collectively contribute to the enhanced binding affinity. Together, our structure data provide a structural basis for the dynamic binding as well as the specificity of CTY and explain of how a single methyl group in CTY improves its potency, which provides new evidence to reveal previously unclear mechanism of translational modulation for future drug design and anti-TB therapy. Furthermore, our sample preparation method may facilitate drug discovery based on the complexes with low water solubility drugs by cryo-EM technique.

DOI: 10.1080/22221751.2021.2022439
PMCID: PMC8786254
PMID: 34935599 [Indexed for MEDLINE]

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

78. **The Application of Artificial Intelligence in the Diagnosis and Drug Resistance Prediction of Pulmonary Tuberculosis.**

Front Med (Lausanne). 2022 Jul 28;9:935080. doi: 10.3389/fmed.2022.935080. eCollection 2022.

Liang S(1)(2), Ma J(3), Wang G(2), Shao J(1), Li J(1), Deng H(1)(2), Wang C(1), Li W(1).

With the increasing incidence and mortality of pulmonary tuberculosis, in addition to tough and controversial disease management, time-wasting and resource-limited conventional approaches to the diagnosis and differential diagnosis of tuberculosis are still awkward issues, especially in countries with high tuberculosis burden and backwardness. In the meantime, the climbing proportion of drug-resistant tuberculosis poses a significant hazard to public health. Thus, auxiliary diagnostic tools with higher efficiency and accuracy are urgently required. Artificial intelligence (AI), which is not new but has recently grown in popularity, provides researchers with opportunities and technical underpinnings to develop novel, precise, rapid, and automated implements for pulmonary tuberculosis care, including but not limited to tuberculosis detection. In this review, we aimed to introduce representative AI methods, focusing on deep learning and radiomics, followed by definite descriptions of the state-of-the-art AI models developed using medical images and genetic data to detect pulmonary tuberculosis, distinguish the infection from other pulmonary diseases, and identify drug resistance of tuberculosis, with the purpose of assisting physicians in deciding the appropriate therapeutic schedule in the early stage of the disease. We also enumerated the challenges in maximizing the impact of AI in this field such as generalization and clinical utility of the deep learning models.

DOI: 10.3389/fmed.2022.935080
PMCID: PMC9366014
PMID: 35966878

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

79. **Superior Efficacy of a TBI-166, Bedaquiline, and Pyrazinamide Combination Regimen in a Murine Model of Tuberculosis.**

Antimicrob Agents Chemother. 2022 Aug 4:e0065822. doi: 10.1128/aac.00658-22. Online ahead of print.

Ding Y(#)(1), Zhu H(#)(1), Fu L(1), Zhang W(1), Wang B(1), Guo S(1), Chen X(1), Wang N(1), Liu H(1), Lu Y(1).

TBI-166, derived from riminophenazine analogues, shows more potent anti-TB activity than clofazimine and is being assessed against tuberculosis (TB) in a phase IIa clinical trial in China. Preclinical regimen studies containing TBI-166 will support the phase IIb clinical trials of TBI-166. In the present study, we compared the efficacy in three murine TB models of an all-oral drug-resistant TB drug regimen of TBI-166 with bedaquiline (BDQ) and pyrazinamide (PZA) with the first-line regimen of isoniazid (INH) with rifampin (RFP) and PZA (HRZ regimen), the most effective reported TBI-166-containing regimen of TBI-166 with BDQ and linezolid (LZD), and the Nix-TB clinical trial regimen of BDQ with pretomanid and LZD (BPaL regimen). In the C3HeB/FeJ murine TB model, for the TBI-166+BDQ+PZA regimen, the lungs of mice were culture negative at 4 weeks, and there were no relapses at 8 weeks of treatment. The reduction in bacterial burden and relapse rate were greater than those of the HRZ regimen and the TBI-166+BDQ+LZD regimen. Compared with the BPaL regimen, the TBI-166+BDQ+PZA regimen had similar or stronger early bactericidal activity, bactericidal activity, and sterilizing activity in the BALB/c murine TB model. The bacterial burden in the TBI-166+BDQ+PZA regimen group decreased significantly more than that in the BPaL regimen group and was almost or totally relapse free (<13.33% after 8 weeks). In conclusion, oral short-course three-drug regimens, including TBI-166 with high efficacy, were identified. The TBI-166+BDQ+PZA regimen is recommended for further study in a TBI-166 phase IIb clinical trial.

DOI: 10.1128/aac.00658-22
PMID: 35924925

80. **Pharmacogenetic testing for NAT2 genotypes in a Tanzanian population across the lifespan to guide future personalized isoniazid dosing.**

Tuberculosis (Edinb). 2022 Aug 8;136:102246. doi: 10.1016/j.tube.2022.102246. Online ahead of print.

Masiphephethu MV(1), Sariko M(2), Walongo T(3), Maro A(2), Mduma D(2), Gratz J(4), Alshaer M(5), Peloquin CA(5), Mduma E(3), Mpagama SG(6), Thomas T(4), Houpt ER(4), Traore A(1), Bessong P(1), Heysell SK(7), Operario DJ(4).

Despite updated recommendations for weight-based isoniazid dosing in children with drug-susceptible tuberculosis (TB) and higher dose isoniazid in regimens for adults with drug-resistant TB, individual pharmacokinetic variability can lead to sub-target isoniazid exposure. Host pharmacogenetics and isoniazid exposure remain understudied, especially in the East African population. We therefore employed a real-time polymerase chain reaction (qPCR) assay system to test genomic DNA extracted from saliva samples targeting the NAT2 gene responsible for isoniazid metabolism to describe the frequency of human single nucleotide polymorphisms in NAT2 within populations of children and adults in Tanzania, ascribe those polymorphisms to acetylator phenotype, and correlate to serum isoniazid exposures. In adults treated with higher dose isoniazid, genotypes with a predicted allelic phenotype of slow or intermediate acetylation were able to achieve a 0.41 μg/mL higher Cmax ($p = 0.018$) and a 2.9h*μg/mL higher AUC0-12 ($p = 0.003$) per mg/kg increase in isoniazid dosage versus adults with rapid acetylation phenotype. A similar relationship was not found in the younger age population as predicted by timing of NAT2 maturation. This saliva based qPCR assay was fieldable to guide personalized isoniazid dosing in adults but not young children that may not have full NAT2 maturation and activity.

DOI: 10.1016/j.tube.2022.102246
PMID: 35961094

81. **Design, synthesis and biological evaluation of (Quinazoline 4-yloxy)acetamide and (4-oxoquinazoline-3(4H)-yl)acetamide derivatives as inhibitors of Mycobacterium tuberculosis bd oxidase.**

Eur J Med Chem. 2022 Aug 6;242:114639. doi: 10.1016/j.ejmech.2022.114639. Online ahead of print.

Kumar A(1), Kumari N(2), Bhattacherjee S(1), Venugopal U(2), Parwez S(3), Siddiqi MI(3), Krishnan MY(4), Panda G(5).

New chemical scaffolds with novel mechanism of action are urgently needed for the treatment of drug resistant tuberculosis. The oxidative phosphorylation

pathway of Mycobacterium tuberculosis consists of multiple clinically validated drug targets. This pathway can function through any one of the two terminal oxidases-the proton pumping cytochrome bc1-aa3 supercomplex, or the less energy efficient but high affinity cytochrome bd oxidase. Inhibiting the bc1 complex alone has been found bacteriostatic and not bactericidal. On the other hand, inhibition of both these oxidases turns lethal to the pathogen. In the present study, we used a bc1 complex mutant of M. tuberculosis to screen (Quinazoline 4-yloxy)acetamide and (4-oxoquinazoline-3(4H)-yl)acetamide derivatives against the alternate oxidase, i.e., cytochrome bd oxidase. Two molecules, S-021-0601 and S-021-0607 were found to inhibit the mutant with MICs 8 and 16 μM respectively, compared to MICs of 128 and 256 μM against the wild type M. tuberculosis. In the wild type, one of the compounds showed synergism with Q203, an inhibitor of bc1 complex, in inhibiting growth under aerobic conditions. Both compounds showed synergism with Q203 in depleting bacterial ATP and inhibiting oxygen consumption. Both the compounds at 32 μM (one-fourth or one-eighth of their MICs for wild type) were bactericidal to wild type bacteria under hypoxic condition, causing ∼1.9 log10 reduction in viable counts which increased to ∼4-log10 when combined with Q203.

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PMID: 35973312

82. **Moxifloxacin-Mediated Killing of Mycobacterium tuberculosis Involves Respiratory Downshift, Reductive Stress, and Accumulation of Reactive Oxygen Species.**

Antimicrob Agents Chemother. 2022 Aug 17:e0059222. doi: 10.1128/aac.00592-22. Online ahead of print.

Shee S(#)(1)(2), Singh S(#)(1)(2), Tripathi A(1)(2), Thakur C(3), Kumar T A(4), Das M(1)(2), Yadav V(1)(2), Kohli S(1)(2), Rajmani RS(2), Chandra N(3), Chakrapani H(4), Drlica K(5), Singh A(1)(2).

Moxifloxacin is central to treatment of multidrug-resistant tuberculosis. Effects of moxifloxacin on the Mycobacterium tuberculosis redox state were explored to identify strategies for increasing lethality and reducing the prevalence of extensively resistant tuberculosis. A noninvasive redox biosensor and a reactive oxygen species (ROS)-sensitive dye revealed that moxifloxacin induces oxidative stress correlated with M. tuberculosis death. Moxifloxacin lethality was mitigated by supplementing bacterial cultures with an ROS scavenger (thiourea), an iron chelator (bipyridyl), and, after drug removal, an antioxidant enzyme (catalase). Lethality was also reduced by hypoxia and

nutrient starvation. Moxifloxacin increased the expression of genes involved in the oxidative stress response, iron-sulfur cluster biogenesis, and DNA repair. Surprisingly, and in contrast with Escherichia coli studies, moxifloxacin decreased expression of genes involved in respiration, suppressed oxygen consumption, increased the NADH/NAD+ ratio, and increased the labile iron pool in M. tuberculosis. Lowering the NADH/NAD+ ratio in M. tuberculosis revealed that NADH-reductive stress facilitates an iron-mediated ROS surge and moxifloxacin lethality. Treatment with N-acetyl cysteine (NAC) accelerated respiration and ROS production, increased moxifloxacin lethality, and lowered the mutant prevention concentration. Moxifloxacin induced redox stress in M. tuberculosis inside macrophages, and cotreatment with NAC potentiated the antimycobacterial efficacy of moxifloxacin during nutrient starvation, inside macrophages, and in mice, where NAC restricted the emergence of resistance. Thus, NADH-reductive stress contributes to moxifloxacin-mediated killing of M. tuberculosis, and the respiration stimulator (NAC) enhances lethality and suppresses the emergence of drug resistance.

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PMID: 35975988

83. **Discovery of newer pyrazole derivatives with potential anti-tubercular activity via 3D-QSAR based pharmacophore modelling, virtual screening, molecular docking and molecular dynamics simulation studies.**

Mol Divers. 2022 Aug 15. doi: 10.1007/s11030-022-10511-8. Online ahead of print.

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Tuberculosis is one of the leading causes of death of at least one million people annually. The deadliest infectious disease has caused more than 120 million deaths in humans since 1882. The cell wall structure of Mycobacterium tuberculosis is important for survival in the host environment. InhA is the foremost target for the development of novel anti-tubercular agents. Therefore, we report pharmacophore-based virtual screening (ZINC and ASINEX databases) and molecular docking study (PDB Code: 4TZK) to identify and design potent inhibitors targeting to InhA. A five-point pharmacophore model AADHR_1 (with R2 = 0.97 and Q2 = 0.77) was developed by using 47 compounds with its reported MIC values. Further, to identify and design potent hit molecules based on lead identification and modification, generated hypothesis employed for virtual screening using ZINC and ASINEX databases. Predicted pyrazole derivatives further gauged for drug likeliness and docked against enoyl acyl carrier protein reductase to categorize the essential amino acid interactions to the active site of the enzyme. Structure elucidation of these synthesized compounds was carried

out using IR, MS, 1H-NMR and 13C-NMR spectroscopy. Amongst all the synthesized compounds, some of the compounds 5a, 5c, 5d and 5e were found to be potent with their MIC ranging from 2.23 to 4.61 µM. Based on preliminary anti-tubercular activity synthesized potent molecules were further assessed for MDR-TB, XDR-TB and cytotoxic study.

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PMID: 35969333

84. **The case for expanding worldwide access to point of care molecular drug susceptibility testing for isoniazid.**

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Vogensen VB(1), Anthony RM(2), Kerstjens HAM(1), Tiberi S(3), de Steenwinkel JEM(4), Akkerman OW(5).

DOI: 10.1016/j.cmi.2022.03.033
PMID: 35378271 [Indexed for MEDLINE]

85. **ALB, HP, OAF and RBP4 as novel protein biomarkers for identifying cured patients with pulmonary tuberculosis by DIA.**

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Lu Q(1), Liu J(2), Yu Y(1), Liang HF(3), Zhang SQ(2), Li ZB(4), Chen JX(5), Xu QG(3), Li JC(6).

BACKGROUND: Pulmonary tuberculosis (TB) is a serious infectious disease that lacks robust blood-based biomarkers to identify cured TB. Some discharged patients are not fully cured and may relapse or even develop multidrug-resistant TB. This study is committed to finding proteomic-based plasma biomarkers to support establishing laboratory standards for clinical TB cure.
METHODS: Data-independent acquisition (DIA) was used to obtain the plasma protein expression profiles of TB patients at different treatment stages compared with healthy controls. Multivariate statistical methods and bioinformatics were used to analyze the data.

RESULTS: Bioinformatic analysis suggests coagulation dysfunction and vitamin and lipid metabolism disturbances in TB. Albumin (ALB), haptoglobin (HP), out at first protein homolog (OAF), and retinol-binding protein 4 (RBP4) can be used to establish a diagnostic model for the efficacy evaluation of TB with an area under the curve of 0.963, which could effectively distinguish untreated TB patients from cured patients.
CONCLUSIONS: Our research demonstrated that ALB, HP, OAF and RBP4 can be potential biomarkers for evaluating the efficacy of TB. These findings may provide experimental data for establishing the laboratory indicators of clinical TB cure and providing clinicians with new targets for exploring the underlying mechanisms of TB pathogenesis.

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

86. **Anemia with elevation of growth differentiation factor-15 level in linezolid treated multidrug-resistant tuberculosis: Case series of three patients.**

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Oehadian A(1)(2), Santoso P(3), Menzies D(4), Ruslami R(5).

Linezolid is now recommended as a first line drug for Multidrug Resistant Tuberculosis (MDR-TB). Previous studies reported hematologic toxicity as one of the main side effects. The mechanism of this toxicity is mitochondrial dysfunction, for which a biomarker is Growth differentiation factor-15 (GDF-15). There is no previous report about GDF-15 and its association with hematologic toxicity from Linezolid in the treatment of MDR-TB. We present three cases of MDR-TB involving severe anemia associated with linezolid who had GDF-15 elevation. These cases highlight the need for more research into the relationship between GDF-15 and hematologic toxicity in MDR-TB patients treated with linezolid.

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PMID: 35957807

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