Literature

1. **Spatial heterogeneity of extensively drug resistant-tuberculosis in Western Cape Province, South Africa.**

Sci Rep. 2022 Jun 27;12(1):10844. doi: 10.1038/s41598-022-14581-4.

Sy KTL(1), Leavitt SV(2), de Vos M(3), Dolby T(4), Bor J(1)(2), Horsburgh CR Jr(1)(2)(5)(6), Warren RM(3), Streicher EM(3), Jenkins HE(2), Jacobson KR(7).

Tuberculosis (TB) remains a leading infectious disease killer globally. Treatment outcomes are especially poor among people with extensively drug-resistant (XDR) TB, until recently defined as rifampicin-resistant (RR) TB with resistance to an aminoglycoside (amikacin) and a fluoroquinolone (ofloxacin). We used laboratory TB test results from Western Cape province, South Africa between 2012 and 2015 to identify XDR-TB and pre-XDR-TB (RR-TB with resistance to one second-line drug) spatial hotspots. We mapped the percentage and count of individuals with RR-TB that had XDR-TB and pre-XDR-TB across the province and in Cape Town, as well as amikacin-resistant and ofloxacin-resistant TB. We found the percentage of pre-XDR-TB and the count of XDR-TB/pre-XDR-TB highly heterogeneous with geographic hotspots within RR-TB high burden areas, and found hotspots in both percentage and count of amikacin-resistant and ofloxacin-resistant TB. The spatial distribution of percentage ofloxacin-resistant TB hotspots was similar to XDR-TB hotspots, suggesting that fluoroquinolone-resistace is often the first step to additional resistance. Our work shows that interventions used to reduce XDR-TB incidence may need to be targeted within spatial locations of RR-TB, and further research is required to understand underlying drivers of XDR-TB transmission in these locations.

DOI: 10.1038/s41598-022-14581-4
PMCID: PMC9237070
PMID: 35760977 [Indexed for MEDLINE]

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

2. **Bedaquiline, Delamanid, Linezolid and Clofazimine for Treatment of Pre-extensively Drug-Resistant Tuberculosis.**

Clin Infect Dis. 2022 Jun 29:ciac528. doi: 10.1093/cid/ciac528. Online ahead of print.

Padmapriyadarsini C(1), Vohra V(2), Bhatnagar A(3), Solanki R(4), Sridhar R(5), Anande L(6), Muthuvijaylakshmi M(1), Bhatia M(2), Jeyadeepa B(1), Taneja G(3), Balaji S(1), Shah P(4), Saravanan N(1), Chauhan V(6), Kumar H(1), Ponnuraja C(1), Livchits V(7), Bahl M(8), Alavadi U(7), Sachdeva KS(9), Swaminathan S(10)(11); for BEAT India Team.

BACKGROUND: Treatment success rates for multidrug-resistant tuberculosis (MDR-TB) remain low globally. Availability of newer drugs has given scope to develop regimens that can be patient-friendly, less toxic, with improved outcomes. We proposed to determine the effectiveness of an entirely oral, short-course regimen with Bedaquiline and Delamanid in treating MDR-TB with additional resistance to fluoroquinolones (MDR-TBFQ+) or second-line injectable (MDR-TBSLI+).
METHODS: We prospectively determined the effectiveness and safety of combining two new drugs with two repurposed drugs - Bedaquiline, Delamanid, Linezolid, and Clofazimine for 24-36 weeks in adults with pulmonary MDR-TBFQ+ or/and MDR-TBSLI+. The primary outcome was a favorable response at end of treatment, defined as two consecutive negative cultures taken four weeks apart. The unfavorable outcomes included bacteriologic or clinical failure during treatment period.
RESULTS: Of the 165 participants enrolled, 158 had MDR-TBFQ+. At the end of treatment, after excluding 12 patients due to baseline drug susceptibility and culture negatives, 139 of 153 patients (91%) had a favorable outcome. Fourteen patients (9%) had unfavorable outcomes: four deaths, seven treatment changes, two bacteriological failures, and one withdrawal. During treatment, 85 patients (52%) developed myelosuppression, 69 (42%) reported peripheral neuropathy, and none had QTc(F) prolongation >500msec. At 48 weeks of follow-up, 131 patients showed sustained treatment success with the resolution of adverse events in the majority.
CONCLUSION: After 24-36 weeks of treatment, this regimen resulted in a satisfactory favorable outcome in pulmonary MDR-TB patients with additional drug resistance. Cardiotoxicity was minimal, and myelosuppression, while common, was detected early and treated successfully.

DOI: 10.1093/cid/ciac528
PMID: 35767251

3. **Recognition of specific immunogenic antigens with potential diagnostic value in multi-drug resistant Mycobacterium tuberculosis inducing humoral immunity in MDR-TB patients.**

Infect Genet Evol. 2022 Jul 3;103:105328. doi: 10.1016/j.meegid.2022.105328. Online ahead of print.

Hadizadeh Tasbiti A(1), Badmasti F(2), Siadat SD(1), Fateh A(1), Yari F(3), GHzanfari Jajin M(4), Yari S(5).

Tuberculosis (TB) as a public health crisis is caused by the intracellular bacterium Mycobacterium tuberculosis. Detection of immunogenic proteins in TB is valuable for the development of diagnostic tests, vaccine formulations and monitoring treatment outcome. In this study, we differentiated the immune-reactivity of proteins in multidrug-resistant tuberculosis (MDRTB) and drug-susceptible strains using purified anti-MDRTB antibodies isolated from inpatients. Our data showed that the anti- MDRTB antibody was well able to detect the MDR strain in the patient's sputum. The immunogenic proteins of MDRTB were purified by affinity chromatography and subjected to matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectrometry. Analysis of the data revealed that seven MDRTB immunogenic proteins, including Rv2986c (HupB), Rv3699, Rv1133c (MetE), Rv0440 (GroEL), Rv3057c, Rv2558 and Rv2971 are involved in DNA stability, metabolism, cellular processes and some unknown functions. Similarities in the electrophoresis protein profiles were evident between the extracts of MDR and sensitive TB strains. However, the protein expression patterns of MDRTB isolates were distinguishable from that formed by susceptible TB strains.

DOI: 10.1016/j.meegid.2022.105328
PMID: 35788051

4. **Prevalence of multidrug-resistant tuberculosis in East Africa: A systematic review and meta-analysis.**

PLoS One. 2022 Jun 30;17(6):e0270272. doi: 10.1371/journal.pone.0270272. eCollection 2022.

Molla KA(1), Reta MA(2), Ayene YY(1).

BACKGROUND: The rate of multidrug-resistant tuberculosis is increasing at an alarming rate throughout the world. It is becoming an emerging public health problem in East Africa. The prevalence of multidrug-resistant tuberculosis among pulmonary tuberculosis positive individuals in the region has not been thoroughly investigated.

AIM: The aim of this systematic review and meta-analysis is to estimate the pooled prevalence of multidrug-resistant tuberculosis among newly diagnosed and previously treated pulmonary tuberculosis cases in East African countries.
METHODS: English published articles were systematically searched from six electronic databases: PubMed, EMBASE, Scopus, Science direct, Web of Science, and Google scholar. The pooled prevalence of multidrug-resistant tuberculosis and associated risk factors were calculated using Der Simonian and Laird's random Effects model. Funnel plot symmetry visualization confirmed by Egger's regression asymmetry test and Begg rank correlation methods was used to assess publication bias. A total of 16 articles published from 2007 to 2019 were included in this study. STATA 14 software was used for analysis.
RESULTS: Out of 1025 articles identified citations, a total of 16 articles were included in final meta-analysis. The pooled prevalence of multidrug-resistant tuberculosis among newly diagnosed tuberculosis cases and previously treated tuberculosis patients was 4% (95%CI = 2-5%) and 21% (95%CI: 14-28%), respectively. Living conditions, lifestyles (smoking, alcohol use, and drug abuse), previous medical history, diabetes history, and human immunodeficiency virus infection were risk factors contributing to the higher prevalence of multidrug-resistant tuberculosis in East Africa.
CONCLUSION: The review found a significant prevalence of multidrug-resistant tuberculosis in the region. An early diagnosis of tuberculosis and rapid detection of drug-resistant Mycobacterium tuberculosis is a critical priority to identify patients who are not responding to the standard treatment and to avoid transmission of resistant strains. It is also very important to strengthen tuberculosis control and improve monitoring of chemotherapy.

DOI: 10.1371/journal.pone.0270272
PMCID: PMC9246177
PMID: 35771884 [Indexed for MEDLINE]

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

5. **Impacts of clofazimine on the treatment outcomes of drug-resistant tuberculosis.**

Microbes Infect. 2022 Jul 2:105020. doi: 10.1016/j.micinf.2022.105020. Online ahead of print.

Wang MG(1), Liu XM(2), Wu SQ(1), He JQ(3).

BACKGROUND: The purpose of this research was to evaluate the effect of clofazimine on drug-resistant tuberculosis treatment outcomes.
METHODS: A systematic search was conducted in the PubMed, Web of Science and

EMBASE databases to identify eligible studies published up to July 10, 2021. The search terms were as follows: "clofazimine," "tuberculosis," "multidrug resistant tuberculosis" or "extensively drug resistant tuberculosis" and their synonyms or similar words. Two researchers independently screened the titles, abstracts, and full texts for inclusion. Meta-analysis was performed with Stata version 16.0 (Stata Corp., College Station, Texas, USA). Risk ratios (RRs) with 95% CIs were calculated to evaluate the treatment outcome.
RESULTS: Eight studies including 3,219 participants were included in the meta-analysis. The meta-analysis found that the rates of treatment completion was higher in patients receiving clofazimine-containing regimens than in those not receiving clofazimine-containing regimens (RR: 1.185 (1.060-1.325), P = 0.003). Significant reduction in treatment failure (RR: 0.598 (0.473-0.756), P < 0.001) was found in the clofazimine treatment group. The subgroup analyses of randomized controlled trials (RCTs) found a higher rates of favorable outcomes, treatment completion and cure in the clofazimine group than in the control group (RR: 1.203 (1.029-1.407), P = 0.020; RR: 3.167 (2.043-4.908), P < 0.001; and RR: 1.251 (1.031-1.518), P = 0.023, respectively). Patients receiving clofazimine had a lower risk of treatment failure than those not receiving clofazimine (RR: 0.529 (0.454-0.616), P < 0.001). However, clofazimine treatment did not have a statistically significant effect on all-cause mortality in RCTs.
CONCLUSIONS: This study demonstrated that compared with patients who do not receive clofazimine, this drug has the potential to achieve a higher favorable outcome, treatment completion and cure rates, and a lower treatment failure risk among drug-resistant tuberculosis cases.

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PMID: 35792202

Conflict of interest statement: Declaration of Competing Interest The authors declare no conflicts of interest.

6. **[Prevalence and transmission of pyrazinamide-resistant Mycobacterium tuberculosis in Hunan Province,China].**

Zhonghua Jie He He Hu Xi Za Zhi. 2022 Jul 12;45(7):677-685. doi: 10.3760/cma.j.cn112147-20211219-00904.

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

Liu BB(1), Hu PL(1), Chen ZH(1), Yi SL(1), Zhang XP(1), Tan YH(1).

Objective: To provide a scientific reference for the prevention and treatment of pyrazinamide-resistant tuberculosis (PZA-R TB), we analyzed the prevalence and risk factors of pyrazinamide-resistant tuberculosis in Hunan province and described the genotyping and clustering characteristics of the pyrazinamide-resistant Mycobacterium tuberculosis (PZA-R MTB) isolates. Methods: The drug susceptibility test results of first-line anti-tuberculosis drugs including isoniazid (INH), rifampicin (RFP), streptomycin (SM), ethambutol (EMB) and pyrazinamide (PZA), and the characteristics of patients were collected from 3 862 tuberculosis patients in Hunan Chest Hospital (Institute of Tuberculosis Control and Prevention) from January 2016 to December 2018. The prevalence of PZA-R TB was calculated and risk factors were analyzed by univariate and multivariable logistic regression analysis. Two hundred and twelve Mycobacterium tuberculosis isolates selected from June 2017 to June 2018 were genotyped using the 24-loci MIRU-VNTR system. The genetic difference value (h), and the Hunter-Gaston index (HGI) were used to evaluate the resolution and variation for the 24 loci. MIRU-VNTR results were analyzed using BioNumerics 5.0 software to conduct cluster analysis. Clustered isolates were further analyzed by pncA gene sequencing. Results: The rate of PZA-R TB among tuberculosis patients and MDR patients was 14.7%(566/3 862) and 60.5%(511/844), respectively. Multivariable logistic regression analysis showed that patients who were INH mono-resistance and MDR had a higher risk of developing PZA resistance, compared with TB patients who were pan-sensitive to anti-TB drugs (INH, RFP, SM, and EMB). The adjusted OR value (95%CI) was 13.08(5.67-30.18), 298.41(164.88-540.08), respectively, and P values were all less than 0.01. Clustering analysis showed that 65 strains formed 19 clusters, the clustering rate was 30.7%(65/212). Of 19 clusters, eight clusters had at least two isolates with identical pncA mutation types within each cluster. In eight clusters, cluster 4, 6, 16 had four, three, and two patients who lived in the same county, respectively, thus providing probable epidemiological links for the recent transmission of PZA-R Mycobacterium tuberculosis. At least 47.6%(101/212) of PZA drug-resistant TB patients were suggestive of primary drug resistance caused by transmission. Conclusions: The prevalence of PZA-R TB was severe in Hunan province. PZA susceptibility testing should be performed for isolates resistant to any first-line anti-tuberculosis drugs, especially for MDR-MTB isolates. Nearly half of tuberculosis patients were suggestive of primary drug resistance caused by transmission. The prevention and treatment strategy of PZA-R TB should focus on the standardized treatment and management of patients as well as control of the source of infection.

DOI: 10.3760/cma.j.cn112147-20211219-00904
PMID: 35768376 [Indexed for MEDLINE]

7. **Acquired bedaquiline resistance in Karakalpakstan, Uzbekistan.**

Int J Tuberc Lung Dis. 2022 Jul 1;26(7):658-663. doi: 10.5588/ijtld.21.0631.

Nair P(1), Hasan T(1), Zaw KK(1), Allamuratova S(1), Ismailov A(1), Mendonca P(1), Bekbaev Z(2), Parpieva N(3), Singh J(1), Sitali N(4), Bermudez-Aza E(5), Sinha A(6).

BACKGROUND: The WHO recommends the use of bedaquiline (BDQ) in longer, as well as shorter, multidrug-resistant TB (MDR-TB) treatment regimens. However, resistance to this new drug is now emerging. We aimed to describe the characteristics of patients in Karakalpakstan, Uzbekistan, who were treated for MDR-TB and acquired BDQ resistance during treatment.METHODS: We performed a retrospective study of routinely collected data for patients treated for MDR-TB in Karakalpakstan between January 2015 and December 2020. We included patients on BDQ-containing regimens with baseline susceptibility to BDQ who developed BDQ resistance at any point after treatment initiation. Patients resistant to BDQ at baseline or with no confirmed susceptibility to BDQ at baseline were excluded.RESULTS: Of the 523 patients who received BDQ-containing regimens during the study period, BDQ resistance was detected in 31 patients (5.9%); 20 patients were excluded-16 with no prior confirmation of BDQ susceptibility and 4 who were resistant at baseline. Eleven patients with acquired BDQ resistance were identified. We discuss demographic variables, resistance profiles, treatment-related variables and risk factors for unfavourable outcomes for these patients.CONCLUSION: Our programmatic data demonstrated the acquisition of BDQ resistance during or subsequent to receiving a BDQ-containing regimen in a patient cohort from Uzbekistan. We highlight the need for individualised treatment regimens with optimised clinical and laboratory follow up to prevent resistance acquisition.

DOI: 10.5588/ijtld.21.0631
PMCID: PMC9272738
PMID: 35768925 [Indexed for MEDLINE]

8. **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

9. **WHO drug-resistant TB guidelines 2022: what is new?**

Int J Tuberc Lung Dis. 2022 Jul 1;26(7):590-591. doi: 10.5588/ijtld.22.0263.

Migliori GB(1), Tiberi S(2).

DOI: 10.5588/ijtld.22.0263
PMID: 35768917 [Indexed for MEDLINE]

10. **Determinants of Multidrug-Resistant Mycobacterium tuberculosis Infection: A Multicenter Study from Southern Ethiopia.**

Infect Drug Resist. 2022 Jul 5;15:3523-3535. doi: 10.2147/IDR.S363628.
eCollection 2022.

Badgeba A(1), Shimbre MS(2), Gebremichael MA(3), Bogale B(4), Berhanu M(5), Abdulkadir H(6).

BACKGROUND: Multidrug-resistant tuberculosis (MDR-TB) continues to be a public health problem. Globally in 2019, a total of 465,000 people developed rifampicin-resistant TB (RR-TB), of which 78% had MDR-TB. There is a paucity of evidence on the determinants of MDR-TB in southern Ethiopia. Hence, this study aimed to assess the determinants of MDR-TB in southern Ethiopia.
METHODS: A hospital-based case-control study was conducted in southern Ethiopia. The cases were all MDR-TB patients attending TB clinics, and controls were all patients who were declared as cured or treatment completed. The cases were selected by consecutive sampling, and a simple random sampling technique was used for controls. Multivariable logistic regression analysis was done to identify determinants of MDR-TB. Adjusted odds ratios (AORs) with 95% confidence intervals (CIs) were computed, and statistical significance was declared at a P-value less than 5%.
RESULTS: A total of 191 participants, 67 cases, and 124 controls were included. TB patients facing social stigma (AOR = 8.9, 95% CI: 2.3-34.6), living in a household with one room (AOR = 12.3, 95% CI: 2.3-63.5), and two rooms (AOR = 9.7, 95% CI: 1.7-54.8), having the previous history of TB treatment (AOR = 11.8, 95% CI: 2.9-47), having baseline body mass index (BMI) less than 18.5Kg/m2(AOR = 4.5, 95% CI: 1.2-16.8), and having pulmonary TB (AOR = 5.1, 95% CI: 1.33-19.8)

were determinants of MDR-TB.
CONCLUSION: In this study, TB patients facing social stigma, living in one- and two-roomed houses, having a previous history of TB treatment, having low baseline BMI and pulmonary type of TB had higher odds of MDR-TB. Therefore, health workers in TB control programs should include mental health services in the TB care protocol, and priority should be given to malnutrition screening as a first-line diagnosis, nutritional supplements, and health education about proper housing.

DOI: 10.2147/IDR.S363628
PMCID: PMC9270894
PMID: 35818450

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

11. **25 years of surveillance of drug-resistant tuberculosis: achievements, challenges, and way forward.**

Lancet Infect Dis. 2022 Jul;22(7):e191-e196. doi: 10.1016/S1473-3099(21)00808-2. Epub 2022 Mar 3.

Dean AS(1), Tosas Auguet O(2), Glaziou P(2), Zignol M(2), Ismail N(2), Kasaeva T(2), Floyd K(2).

Comment in
Lancet Infect Dis. 2022 Jun;22(6):760.

Tuberculosis is second only to COVID-19 as a cause of death from a single infectious agent. In 2020, almost 10 million people were estimated to have developed tuberculosis and it caused 1·5 million deaths. Around a quarter of deaths caused by antimicrobial resistance are due to rifampicin-resistant tuberculosis. Antimicrobial resistance surveillance systems for many bacterial pathogens are still in the early stages of implementation in many countries, and do not yet allow for the estimation of disease burden at the national level. In this Personal View, we present the achievements, challenges, and way forward for the oldest and largest global antimicrobial resistance surveillance system. Hosted by WHO since 1994, the Global Project on Anti-Tuberculosis Drug Resistance Surveillance has served as a platform for the evaluation of the trends in anti-tuberculosis drug resistance for over 25 years at country, regional, and global levels. With an estimated 465 000 incident cases of

multidrug-resistant and rifampicin-resistant tuberculosis in 2019, drug-resistant tuberculosis remains a public health crisis. The COVID-19 pandemic has reversed years of progress in providing essential tuberculosis services and reducing disease burden. The number of people diagnosed with drug-resistant tuberculosis has dropped by 22% since before the pandemic, and the number of patients provided with treatment for drug-resistant tuberculosis has dropped by 15%. Now more than ever, closing gaps in the detection of drug-resistant tuberculosis requires investment in research and development of new diagnostic tools and their rollout, expansion of sample transport systems, and the implementation of data connectivity solutions.

DOI: 10.1016/S1473-3099(21)00808-2
PMCID: PMC8893725
PMID: 35248168 [Indexed for MEDLINE]

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

12. **Whole-Genome Sequencing for Resistance Level Prediction in Multidrug-Resistant Tuberculosis.**

Microbiol Spectr. 2022 Jun 29;10(3):e0271421. doi: 10.1128/spectrum.02714-21. Epub 2022 Jun 6.

Li J(#)(1), Yang T(#)(2), Hong C(1), Yang Z(1), Wu L(1), Gao Q(2), Yang H(1), Tan W(1).

Defining the precise relationship between resistance mutations and quantitative phenotypic drug susceptibility testing will increase the value of whole-genome sequencing (WGS) for predicting tuberculosis drug resistance. However, a large number of WGS data sets currently lack corresponding quantitative phenotypic data-the MICs. Using MYCOTBI plates, we determined the MICs to nine antituberculosis drugs for 154 clinical multidrug-resistant tuberculosis isolates from the Shenzhen Center for Chronic Disease Control in Shenzhen, China. Comparing MICs with predicted drug-resistance profiles inferred by WGS showed that WGS could predict the levels of resistance to isoniazid, rifampicin, streptomycin, fluoroquinolones, and aminoglycosides. We also found some mutations that may not be associated with drug resistance, such as EmbB D328G, mutations in the gid gene, and C-12T in the eis promoter. However, some strains carrying the same mutations showed different levels of resistance to the

corresponding drugs. The MICs of different strains with the RpsL K88R, fabG1 C-15T mutations and some with mutations in embB and rpoB, had MICs to the corresponding drugs that varied by 8-fold or more. This variation is unexplained but could be influenced by the bacterial genetic background. Additionally, we found that 32.3% of rifampicin-resistant isolates were rifabutin-susceptible, particularly those with rpoB mutations H445D, H445L, H445S, D435V, D435F, L452P, S441Q, and S441V. Studying the influence of bacterial genetic background on the MIC and the relationship between rifampicin-resistant mutations and rifabutin resistance levels should improve the ability of WGS to guide the selection of medical treatment regimens. IMPORTANCE Whole-genome sequencing (WGS) has excellent potential in drug-resistance prediction. The MICs are essential indications of adding a particular antituberculosis drug dosage or changing the entire treatment regimen. However, the relationship between many known drug-resistant mutations and MICs is unclear, especially for rarer ones. The results showed that WGS could predict resistance levels to isoniazid, rifampicin, streptomycin, fluoroquinolones, and aminoglycosides. However, some mutations may not be associated with drug resistance, and some others may confer various MICs to strains carrying them. Also, 32.3% of rifampicin (RIF)-resistant strains were classified as sensitive to rifabutin (RFB), and some mutations in the rpoB gene may be associated with this phenotype. Our data on the MIC distribution of strains with some rarer mutations add to the accumulated data on the resistance level associated with such mutations to help guide further research and draw meaningful conclusions.

DOI: 10.1128/spectrum.02714-21
PMCID: PMC9241708
PMID: 35658579 [Indexed for MEDLINE]

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

13. **Mycobacterium tuberculosis Lineages Associated with Mutations and Drug Resistance in Isolates from India.**

Microbiol Spectr. 2022 Jun 29;10(3):e0159421. doi: 10.1128/spectrum.01594-21. Epub 2022 Apr 20.

Shanmugam SK(#)(1), Kumar N(#)(2), Sembulingam T(1), Ramalingam SB(1), Selvaraj A(1), Rajendhiran U(1), Solaiyappan S(1), Tripathy SP(1), Natrajan M(1), Chandrasekaran P(1), Swaminathan S(3), Parkhill J(4), Peacock SJ(2), Ranganathan UDK(1).

Current knowledge on resistance-conferring determinants in Mycobacterium tuberculosis is biased toward globally dominant lineages 2 and 4. In contrast,

lineages 1 and 3 are predominant in India. In this study, we performed whole-genome sequencing of 498 MDR M. tuberculosis isolates from India to determine the prevalence of drug resistance mutations and to understand the genomic diversity. A retrospective collection of 498 M. tuberculosis isolates submitted to the National Institute for Research in Tuberculosis for phenotypic susceptibility testing between 2014 to 2016 were sequenced. Genotypic resistance prediction was performed using known resistance-conferring determinants. Genotypic and phenotypic results for 12 antituberculosis drugs were compared, and sequence data were explored to characterize lineages and their association with drug resistance. Four lineages were identified although lineage 1 predominated (43%). The sensitivity of prediction for isoniazid and rifampicin was 92% and 98%, respectively. We observed lineage-specific variations in the proportion of isolates with resistance-conferring mutations, with drug resistance more common in lineages 2 and 3. Disputed mutations (codons 430, 435, 445, and 452) in the rpoB gene were more common in isolates other than lineage 2. Phylogenetic analysis and pairwise SNP difference revealed high genetic relatedness of lineage 2 isolates. WGS based resistance prediction has huge potential, but knowledge of regional and national diversity is essential to achieve high accuracy for resistance prediction. IMPORTANCE Current knowledge on resistance-conferring determinants in Mycobacterium tuberculosis is biased toward globally dominant lineages 2 and 4. In contrast, lineages 1 and 3 are predominant in India. We performed whole-genome sequencing of 498 MDR M. tuberculosis isolates from India to determine the prevalence of drug resistance mutations and to understand genomic diversity. Four lineages were identified although lineage 1 predominated (43%). The sensitivity of prediction for isoniazid and rifampicin was 92% and 98%, respectively. We observed lineage-specific variations in the proportion of isolates with resistance-conferring mutations, with drug resistance more common in lineages 2 and 3. Disputed mutations (codons 430, 435, 445, and 452) in the rpoB gene were more common in isolates other than lineage 2. Phylogenetic analysis and pairwise SNP difference revealed high genetic relatedness of lineage 2 isolates. WGS based resistance prediction has huge potential, but knowledge of regional and national diversity is essential to achieve high accuracy for resistance prediction.

DOI: 10.1128/spectrum.01594-21
PMCID: PMC9241780
PMID: 35442078 [Indexed for MEDLINE]

Conflict of interest statement: The authors declare a conflict of interest. J.P. reports personal fees from Next Gen Diagnostics, outside the submitted work. S.J.P. reports receiving funds from Next Gen Diagnostics, outside the submitted work.

14. **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.

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

Indian J Pediatr. 2022 Jul 4. doi: 10.1007/s12098-022-04290-1. Online ahead of print.

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

DOI: 10.1007/s12098-022-04290-1
PMID: 35781616

16. **Diagnosing osteo-articular tuberculosis and multidrug resistance using real-time polymerase chain reaction and high-resolution melt-curve analysis.**

J Orthop Res. 2022 Jul 3. doi: 10.1002/jor.25410. Online ahead of print.

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

The study evaluated real-time quantitative polymerase chain reaction (qPCR) and high-resolution melt-curve analysis (HRM) for simultaneous diagnosis of osteo-articular tuberculosis (OATB) and drug resistance. Two hundred and fifty synovial fluid and pus specimens (20 confirmed OATB by culture, 130 suspected OATB, and 100 controls) processed in the Department of Medical Microbiology, PGIMER were subjected to qPCR using rpoB, MPB64, and IS6110 genes. All OATB positive specimens were subjected to HRM for detecting resistance to rifampicin and isoniazid. qPCR detected 129/150 OATB cases with a sensitivity of 86% (95% for confirmed and 84.6% for suspected OATB cases) and specificity of 100%. rpoB and MPB64 genes had higher sensitivity than IS6110 (86% vs. 74.6%). HRM reported eight multidrug resistant (MDR), two mono-rifampicin, and five mono-isoniazid resistant cases, all were concordant with gene sequencing. qPCR followed by HRM analysis offer a simple, accurate, and rapid platform for simultaneous detection of OATB and MDR.

DOI: 10.1002/jor.25410
PMID: 35780389

17. **Susceptibility of β-Lactam Antibiotics and Genetic Mutation of Drug-Resistant Mycobacterium tuberculosis Isolates in Korea.**

Tuberc Respir Dis (Seoul). 2022 Jul;85(3):256-263. doi: 10.4046/trd.2021.0175.

Epub 2022 May 19.

Park S(1), Jung J(1), Kim J(1), Han SB(2), Ryoo S(1).

BACKGROUND: Mycobacterium tuberculosis (Mtb) is resistant to the β-lactam antibiotics due to a non-classical transpeptidase in the cell wall with β -lactamase activity. A recent study showed that meropenem combined with a β -lactamase inhibitor clavulanate, was effective in MDR and XDR tuberculosis (TB). However, clavulanate can only be used in drugs containing amoxicillin in Korea. In this study, we investigated the susceptibility and genetic mutations of drug-resistant Mtb isolates to amoxicillin-clavulanate and meropenem-clavulanate to improve the diagnosis and treatment of drug-resistant TB patients.
METHODS: The minimum inhibitory concentration (MIC) of amoxicillin-clavulanate and meropenem-clavulanate was examined by resazurin microtiter assay. We used 82 MDR and 40 XDR strains isolated in Korea and two reference laboratory strains. Mutations of drug targets blaC, blaI, ldtA, ldtB, dacB2, and crfA were analyzed by PCR and DNA sequencing.
RESULTS: The MIC90 values of amoxicillin and meropenem with clavulanate in drug-resistant Mtb isolates were 64 and 16, respectively. Gene mutations related to amoxicillin/clavulanate and meropenem/clavulanate resistance could not be identified, but T448G mutation of was found in the blaC gene related to β-lactam antibiotics high susceptibility.
CONCLUSION: Our results provide clinical consideration of β-lactams in treating drug-resistant TB and potential molecular markers of amoxicillin-clavulanate and meropenem-clavulanate susceptibility.

DOI: 10.4046/trd.2021.0175
PMCID: PMC9263340
PMID: 35586904

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

18. **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 Jul 6:1-455. doi: 10.1080/22221751.2022.2099304. Online ahead of print.

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
PMID: 35792049

19. **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

20. **Mycobacterial Infections of the Hand.**

Hand (N Y). 2022 Jul;17(4):772-779. doi: 10.1177/1558944720940064. Epub 2020 Sep 17.

Bilolikar VK(1), Ilyas AM(1)(2).

BACKGROUND: Hand infections caused by mycobacteria are relatively uncommon compared to infections caused by other pathogens; therefore, much of the available literature consists of case reports and limited case series. Broadly categorized into tuberculous and nontuberculous mycobacterial (NTM) infections, both tuberculous and NTM infections are typically insidious with long incubation periods and with the ability to remain dormant for prolonged periods.
METHODS: We reviewed the most current literature on the epidemiology,

presentations, treatment methods, and resistance patterns of mycobacterial infections of the hand focusing on the indications and outcomes of nonoperative as well as operative interventions.
RESULTS: The worldwide burden of tuberculosis remains high and while the overall rate of new diagnosis drug resistant tuberculosis has been on the decline some regions of the world have demonstrated staggeringly high resistance rates to first-line tuberculosis therapies. Signs and symptoms of mycobacterial hand infection are typically inconsistent, and highly dependent on the specific structures of the hand that are affected; therefore, these infections may mimic other infections of the hand like tenosynovitis, joint space infections, and cutaneous infections. The main stay of treatment remains antimycobacterial therapies including but not limited to rifampin, isoniazid, pyrazinamide, and ethambutol.
CONCLUSIONS: The complications associated with mycobacterial hand infections can be significant. Prompt evaluation, including a thorough history to evaluate for potential exposures to infectious sources, followed by appropriate antibiotic choice and duration, with surgical management as needed, is key to reducing the chance that patients experience lasting effects of the infection.

DOI: 10.1177/1558944720940064
PMCID: PMC9274897
PMID: 32940064 [Indexed for MEDLINE]

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

21. **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]

22. **Clinical standards for drug-susceptible pulmonary TB.**

Int J Tuberc Lung Dis. 2022 Jul 1;26(7):592-604. doi: 10.5588/ijtld.22.0228.

Akkerman OW(1), Duarte R(2), Tiberi S(3), Schaaf HS(4), Lange C(5), Alffenaar JWC(6), Denholm J(7), Carvalho ACC(8), Bolhuis MS(9), Borisov S(10), Bruchfeld J(11), Cabibbe AM(12), Caminero JA(13), Carvalho I(14), Chakaya J(15), Centis R(16), Dalcomo MP(17), D Ambrosio L(18), Dedicoat M(19), Dheda K(20), Dooley KE(21), Furin J(22), García-García JM(23), van Hest NAH(24), de Jong BC(25), Kurhasani X(26), Märtson AG(27), Mpagama S(28), Torrico MM(29), Nunes E(30), Ong CWM(31), Palmero DJ(32), Ruslami R(33), Saktiawati AMI(34), Semuto C(35), Silva DR(36), Singla R(37), Solovic I(38), Srivastava S(39), de Steenwinkel JEM(40), Story A(41), Sturkenboom MGG(9), Tadolini M(42), Udwadia ZF(43), Verhage AR(44), Zellweger JP(45), Migliori GB(16).

BACKGROUND: The aim of these clinical standards is to provide guidance on 'best practice´ for diagnosis, treatment and management of drug-susceptible pulmonary TB (PTB).METHODS: A panel of 54 global experts in the field of TB care, public health, microbiology, and pharmacology were identified; 46 participated in a Delphi process. A 5-point Likert scale was used to score draft standards. The final document represents the broad consensus and was approved by all 46 participants.RESULTS: Seven clinical standards were defined: Standard 1, all patients (adult or child) who have symptoms and signs compatible with PTB should undergo investigations to reach a diagnosis; Standard 2, adequate bacteriological tests should be conducted to exclude drug-resistant TB; Standard 3, an appropriate regimen recommended by WHO and national guidelines for the treatment of PTB should be identified; Standard 4, health education and counselling should be provided for each patient starting treatment; Standard 5, treatment monitoring should be conducted to assess adherence, follow patient progress, identify and manage adverse events, and detect development of resistance; Standard 6, a recommended series of patient examinations should be performed at the end of treatment; Standard 7, necessary public health actions

should be conducted for each patient. We also identified priorities for future research into PTB.CONCLUSION: These consensus-based clinical standards will help to improve patient care by guiding clinicians and programme managers in planning and implementation of locally appropriate measures for optimal person-centred treatment for PTB.

DOI: 10.5588/ijtld.22.0228
PMCID: PMC9272737
PMID: 35768923 [Indexed for MEDLINE]

23. **Investing in drug-resistant tuberculosis household contact management and preventive treatment.**

Lancet Glob Health. 2022 Jul;10(7):e942-e943. doi: 10.1016/S2214-109X(22)00200-5. Epub 2022 May 18.

Hussain H(1), Malik AA(2).

Comment on
Lancet Glob Health. 2022 Jul;10(7):e1034-e1044.

DOI: 10.1016/S2214-109X(22)00200-5
PMID: 35597250 [Indexed for MEDLINE]

Conflict of interest statement: We declare no competing interests.

24. **A multidrug efflux protein in Mycobacterium tuberculosis; tap as a potential drug target for drug repurposing.**

Comput Biol Med. 2022 Jul;146:105607. doi: 10.1016/j.compbiomed.2022.105607. Epub 2022 May 16.

Dwivedi M(1), Mukhopadhyay S(2), Yadav S(3), Dubey KD(3).

Tuberculosis (TB) is a serious communicative disease caused by Mycobacterium tuberculosis. Although there are vaccines and drugs available to treat the disease, they are not efficient, moreover, multidrug-resistant TB (MDR-TB) become a major hurdle in its therapy. These MDR strains utilize the multidrug efflux pump as a decisive weapon to fight against antitubercular drugs. Tap membrane protein was observed as a crucial multidrug efflux pump in M. tuberculosis and its critical implication in MDR-MTB development makes it an effective drug target. In the present study, we have utilized various in silico

approaches to predict the applicability of FDA-approved ion channel inhibitors and blockers as therapeutic leads against Tuberculosis by targeting multidrug efflux protein; Tap in MTB. Tap protein structure is predicted by Phyre2 server followed by model refinement, validation, physio-chemical catheterization and target prediction. Further, the interaction between Tap protein and ligands were analysed by molecular docking and MD simulation run of 100 ns. Based on implication and compatibility, 18 FDA-approved ion channel inhibitors and blockers are selected as a ligand against the Tap protein and eventually observed five ligands; Glimepiride, Flecainide, Flupiritine, Nimodipine and Amlodipine as promising compounds which have exhibited the significant stable interaction with Tap protein and are proposed to modulate or interfere with its activity. These compounds illustrated the substantial docking score and total binding enthalpy more than -7 kcal/mol and -42 kcal/mol respectively which implies that the selected FDA-approved compounds can spontaneously interact with the Tap protein to modulate its function. This study proposed Tap protein as a prominent drug target in MTB and investigated compounds that show considerable interaction with the Tap protein as potential therapeutic molecules. These interactions may lead to modulating or inhibit the activity of drug efflux protein thereby making MTB susceptible to antitubercular drugs.

DOI: 10.1016/j.compbiomed.2022.105607
PMID: 35617724 [Indexed for MEDLINE]

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

Emerg Microbes Infect. 2022 Jun 29:1-45. doi: 10.1080/22221751.2022.2095930. Online ahead of print.

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
PMID: 35765887

26. **Treatment outcomes and associated factors among patients with multidrug-resistant tuberculosis in Ashanti Region, Ghana: a retrospective, cross-sectional study.**

BMJ Open. 2022 Jul 5;12(7):e062857. doi: 10.1136/bmjopen-2022-062857.

Panford V(1), Kumah E(2), Kokuro C(3), Adoma PO(4), Baidoo MA(4), Fusheini A(5), Ankomah SE(5), Agyei SK(6), Agyei-Baffour P(7).

OBJECTIVE: Although several studies have assessed treatment outcomes of drug-susceptible tuberculosis (TB) in Ghana, very little has been done in the area of multidrug-resistant TB (MDR-TB). The aim of this study was to determine treatment outcomes and associated factors among patients treated for MDR-TB in the Ashanti Region, Ghana.
DESIGN: A retrospective, cross-sectional analysis.
SETTING: The study was conducted in the Ashanti Region, the second most populous region in Ghana. The regional MDR-TB register, which contains information on all patients with MDR-TB being treated at the various TB centres in the region, was analysed between February and May 2021.
PARTICIPANTS: The participants consisted of all registered patients with MDR-TB who were placed on treatment between 1 January 2015 and 31 December 2020. Patients were included in the analysis if their treatment outcome had been assigned. Patients with no record of treatment outcome were excluded from the study.
OUTCOME MEASURES: The main outcome variable for the study was MDR-TB treatment outcome, standardised as 'cured', 'treatment completed', 'treatment failure', 'died' and 'lost to follow-up'. A logistic regression model was fitted for

factors associated with the outcome measure.
RESULTS: Out of 159 patients included in the analysis, 86 (54.1%) were declared cured, 28 (17.6%) completed their treatment successfully, 6 (3.8%) were declared treatment failure, 12 (7.5%) were lost to follow-up and 27 (17.0%) died. The overall treatment success rate was 71.7%. Patients who were female (adjusted OR (AOR)=1.27, 95% CI: 1.18 to 1.39, p=0.023), younger (AOR=0.53, 95% CI: 0.19 to 2.11, p=0.012), had a higher level of education (AOR=1.12, 95% CI: 0.65 to 1.90, p=0.034), had a baseline body mass index of 18.5 kg/m2 or above (AOR=1.57, 95% CI: 1.23 to 2.47, p=0.011) and those who did not have a history of TB (AOR=0.47, 95% CI: 0.10 to 0.75, p=0.028) were more likely to have successful MDR-TB treatment outcomes.
CONCLUSIONS: Favourable treatment outcomes for patients with MDR-TB can be achieved in a resource-limited country. Although the recommended WHO target of ≥75% was not met, the current result (71.7% treatment success rate) is still commendable considering all the challenges associated with TB treatment in Ghana.

DOI: 10.1136/bmjopen-2022-062857
PMID: 35790328 [Indexed for MEDLINE]

Conflict of interest statement: Competing interests: None declared.

27. **Resistance and tolerance of Mycobacterium tuberculosis to antimicrobial agents-How M. tuberculosis can escape antibiotics.**

WIREs Mech Dis. 2022 Jun 26:e1573. doi: 10.1002/wsbm.1573. Online ahead of print.

Li H(1), Yuan J(1), Duan S(2), Pang Y(1).

Tuberculosis (TB) poses a serious threat to public health worldwide since it was discovered. Until now, TB has been one of the top 10 causes of death from a single infectious disease globally. The treatment of active TB cases majorly relies on various anti-tuberculosis drugs. However, under the selection pressure by drugs, the continuous evolution of Mycobacterium tuberculosis (Mtb) facilitates the emergence of drug-resistant strains, further resulting in the accumulation of tubercle bacilli with multiple drug resistance, especially deadly multidrug-resistant TB and extensively drug-resistant TB. Researches on the mechanism of drug action and drug resistance of Mtb provide a new scheme for clinical management of TB patients, and prevention of drug resistance. In this

review, we summarized the molecular mechanisms of drug resistance of existing anti-TB drugs to better understand the evolution of drug resistance of Mtb, which will provide more effective strategies against drug-resistant TB, and accelerate the achievement of the EndTB Strategy by 2035. This article is categorized under: Infectious Diseases > Molecular and Cellular Physiology.

DOI: 10.1002/wsbm.1573
PMID: 35753313

28. **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.

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

Bioorg Med Chem Lett. 2022 Jun 28;72:128871. doi: 10.1016/j.bmcl.2022.128871. Online ahead of print.

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

30. **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]

31. **Health-related quality of life of multidrug-resistant tuberculosis patients: A study of eastern Uttar Pradesh, India.**

Indian J Tuberc. 2022 Jul;69(3):347-353. doi: 10.1016/j.ijtb.2021.06.002. Epub 2021 Jun 15.

Venkatesh U(1), Sharma A(2), Srivastava DK(3), Durga R(4).

INTRODUCTION: Much attention has been given to the microbiological aspect, drug treatment, and clinical indicators of MDR-TB, but patients' QOL has remained a neglected area. In this study, we aimed to find the quality of MDRTB on various quality of life domains during the initiation of the MDR Treatment regimen. MATERIALS & METHODS: A cross-sectional study was conducted over a period of 6 months at the Drug-Resistance Tuberculosis Management Centre (DR-TB Centre), of a tertiary care centre in the eastern Uttar pradesh, India. Patients with age >18 years diagnosed with MDR-TB (Multidrug resistance TB) were included in the study. The WHO QOL-BREF scale was used to assess the health-related quality of life of patients. Data were analyzed using SPSS version 21. The institutional ethical review committee approved the study, and consent was taken before the participation of patients.

RESULTS: A total of 157 patients were included in the study & 45.85% were dissatisfied with their condition. Social domain of WHO QOL-BREF is having the lowest mean score (28.51 ± 15.4) while psychological has high mean values (39.92 ± 6.91). There was a significant difference in the physical health domain with respect to age (p-value 0.001). Similar differences have been seen in the psychological domain regarding patient sex (p-value 0.001), smoking and alcohol within the social domain, and loss of income in the environmental domain. CONCLUSION: The mean value of different domains of WHO QOL-BREF is low in MDR-TB patients, with social relation domain being the most affected.

DOI: 10.1016/j.ijtb.2021.06.002
PMID: 35760485 [Indexed for MEDLINE]

Conflict of interest statement: Conflicts of interest The authors have none to declare.

32. **Addressing bedaquiline treatment interruptions in the treatment of drug-resistant TB.**

Int J Tuberc Lung Dis. 2022 Jul 1;26(7):671-677. doi: 10.5588/ijtld.21.0678.

Kambili C(1), Rossenu S(2), Hoetelmans RMW(2), Birmingham E(3), Bakare N(4).

SETTING: The recommended dosing regimen for bedaquiline (BDQ), consisting of a 2-week loading phase (400 mg/day), followed by a maintenance phase (200 mg three times/week), might pose challenges when treatment is interrupted and needs to be reinitiated. Guidance on BDQ treatment re-initiation is, therefore, needed.OBJECTIVE: This pharmacokinetic-based simulation study aimed to provide recommendations for re-initiating BDQ following treatment interruptions.DESIGN: Simulations of treatment interruptions, defined as any time a patient misses ≥2 consecutive BDQ doses for up to 56 consecutive days (2 months), were assessed using the BDQ population-pharmacokinetic model.RESULTS: Any treatment interruption lasting ≤28 days prior to completing the 14-day loading phase can be managed by completing the remaining loading doses. Scenarios when it is sufficient to simply restart maintenance dosing are discussed. In some scenarios, treatment interruptions require reloading for 1 week prior to restarting maintenance dosing.CONCLUSIONS: This simulation study provided recommendations for managing BDQ treatment interruptions and underscores the importance of having a robust population-pharmacokinetic model for TB drugs to inform clinical guidance. Such recommendations are valuable to help ensure optimal treatment with BDQ for treating multidrug-resistant TB.

DOI: 10.5588/ijtld.21.0678
PMCID: PMC9272739
PMID: 35768912 [Indexed for MEDLINE]

33. **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]

34. **Clinical Evaluation of a Line-Probe Assay for Tuberculosis Detection and Drug-Resistance Prediction in Namibia.**

Microbiol Spectr. 2022 Jun 29;10(3):e0025922. doi: 10.1128/spectrum.00259-22. Epub 2022 Jun 7.

Günther G(1)(2)(3), Saathoff E(4)(5), Rachow A(4)(5), Ekandjo H(2), Diergaardt A(2), Marais N(2), Lange C(#)(6)(7)(8)(9), Nepolo E(#)(2).

Treatment of tuberculosis requires rapid information about Mycobacterium tuberculosis (Mtb) drug susceptibility to ensure effective therapy and optimal outcomes. At the tuberculosis referral hospital in Windhoek, Namibia, a country of high tuberculosis incidence, we evaluated the diagnostic accuracy of a line-probe-assay (LPA), GenID, for the molecular diagnosis of Mtb infection and drug resistance in patients with suspected tuberculosis (cohort 1) and confirmed rifampin (RIF)-resistant tuberculosis (cohort 2). GenID test results were compared to Xpert MTB/RIF and/or Mtb culture and antimicrobial suceptibilty testing. GenID LPA was applied to 79 and 55 samples from patients in cohort 1 and cohort 2, respectively. The overall sensitivity of GenID LPA for the detection of Mtb DNA in sputum from patients with detectable and undetectable acid-fast bacilli by sputum smear microscopy was 93.3% (56/60; 95% confidence interval = 83.8-98.2) and 22.7% (5/22; 7.8-45.4). The sensitivity/specificity for the detection of drug resistance was 84.2% (32/38; 68.7-94.0)/100% (19/19; 82.4-100.0) for RIF, 89.7% (26/29; 72.6-97.8)/91.7% (22/24; 73.0-99.0) for isoniazid, and 85.7% (6/7; 42.1-99.6)/94.7% (18/19; 74.0-99.9) for fluoroquinolones; 23.6% of tests for second-line injectable resistance were invalid despite repeat testing. The diagnosis of tuberculosis by detection of Mtb DNA in sputum by GenID LPA depends strongly on the detection of acid-fast bacilli in sputum specimen. Prediction of drug resistance by GenID did not reach the World Health Organization (WHO) target product profile. IMPORTANCE Mycobacterium tuberculosis (Mtb) drug-resistance detection is crucial for successful control of tuberculosis. Line-probe assays (LPA) are frequently used to detect resistance to rifampin, isoniazid, fluoroquinolones (FQs), and second-line injectables (SLIs). GenID RIF/isoniazid (INH), FQ, and SLI LPA have not been widely tested and used so far. This study tested the diagnostic performance of the GenID LPA in a high-incidence TB/HIV, real-world setting in Namibia. The LPA demonstrates only an acceptable diagnostic performance for Mtb and drug-resistance detection. The diagnostic sensitivity and specificity fall short of the WHO suggested target product profiles for LPA.

DOI: 10.1128/spectrum.00259-22
PMCID: PMC9241941
PMID: 35670620 [Indexed for MEDLINE]

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

35. **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]

36. **Practical and psychosocial challenges faced by caregivers influence the acceptability of multidrug-resistant tuberculosis preventive therapy for young children.**

PLoS One. 2022 Jul 14;17(7):e0268560. doi: 10.1371/journal.pone.0268560.

eCollection 2022.

Wademan DT(1), Hoddinott G(1), Purchase SE(1), Seddon JA(1)(2), Hesseling AC(1), Garcia-Prats AJ(1)(3), Reis R(4)(5)(6), Reynolds LJ(7)(8).

Drug-resistant (DR) strains of Mycobacterium tuberculosis (M. tb) are increasingly recognised as a threat to global tuberculosis (TB) control efforts. Identifying people with DR-TB exposure/ infection and providing TB preventive therapy (TPT) is a public health priority. TB guidelines advise the evaluation of household contacts of newly diagnosed TB cases, with the provision of TPT to vulnerable populations, including young children (<5 years). Many children become infected with TB through exposure in their household. Levofloxacin is under evaluation as TPT in children exposed to M. tb strains with resistance to rifampicin and isoniazid (multidrug-resistant TB; MDR-TB). Prior to opening a phase 3 prevention trial in children <5 years exposed to MDR-TB, the pharmacokinetics and safety of a novel formulation of levofloxacin given daily was evaluated as part of a lead-in study. We conducted an exploratory qualitative study of 10 caregivers' experiences of administering this formulation. We explored how the acceptability of levofloxacin as TPT is shaped by the broader impacts of MDR-TB on the overall psychological, social, and financial wellbeing of caregivers, many of whom also had experienced MDR-TB. Caregivers reported that the novel levofloxacin formulation was acceptable. However, caregivers described significant psychosocial challenges in the process of incorporating TPT administration to their children into their daily lives, including financial instability, withdrawal of social support and stigma. When caregivers themselves were sick, these challenges became even more acute. Although new child-friendly formulations can ameliorate some of the pragmatic challenges related to TPT preparation and administration, the overall psychosocial burden on caregivers responsible for administering TPT remains a major determinant of effective MDR-TB prevention in children.

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PMCID: PMC9282439
PMID: 35834509 [Indexed for MEDLINE]

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

37. **K-mer applied in Mycobacterium tuberculosis genome cluster analysis.**

Braz J Biol. 2022 Jun 27;84:e258258. doi: 10.1590/1519-6984.258258. eCollection 2022.

Ferreira LM(1), Sáfadi T(1), Ferreira JL(2).

According to studies carried out, approximately 10 million people developed tuberculosis in 2018. Of this total, 1.5 million people died from the disease. To study the behavior of the genome sequences of Mycobacterium tuberculosis (MTB), the bacterium responsible for the development of tuberculosis (TB), an analysis was performed using k-mers (DNA word frequency). The k values ranged from 1 to 10, because the analysis was performed on the full length of the sequences, where each sequence is composed of approximately 4 million base pairs, k values above 10, the analysis is interrupted, as consequence of the program's capacity. The aim of this work was to verify the formation of the phylogenetic tree in each k-mer analyzed. The results showed the formation of distinct groups in some k-mers analyzed, taking into account the threshold line. However, in all groups, the multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains remained together and separated from the other strains.

DOI: 10.1590/1519-6984.258258
PMID: 35766652 [Indexed for MEDLINE]

38. **Bedaquiline Adherence Measured by Electronic Dose Monitoring Predicts Clinical Outcomes in the Treatment of Patients With Multidrug-Resistant Tuberculosis and HIV/AIDS.**

J Acquir Immune Defic Syndr. 2022 Jul 1;90(3):325-332. doi: 10.1097/QAI.0000000000002940.

O'Donnell MR(1)(2)(3), Padayatchi N(3), Wolf A(1)(2), Zelnick J(4), Daftary A(3)(5), Orrell C(6), Nimmo C(7)(8)(9), Baldwin M(1), Boodhram R(3), Maharaj B(3), Amico KR(10), Naidoo K(3), Friedland G(11).

BACKGROUND: Novel regimens have revolutionized multidrug-resistant tuberculosis (MDR-TB) treatment; however, medication adherence remains challenging and poorly characterized. We hypothesized that bedaquiline adherence, measured using electronic dose monitoring, would predict MDR-TB treatment outcomes.
SETTING: This is a prospective cohort study conducted in KwaZulu-Natal, South Africa.
METHODS: Adults with MDR-TB and HIV initiating bedaquiline and on antiretroviral therapy (ART) were eligible. Separate electronic dose monitoring devices measured bedaquiline and ART adherence through 6 months, calculated as observed versus expected doses. Whole-genome sequencing was performed to identify bedaquiline resistance-associated variants.
RESULTS: From November 2016 through February 2018, 199 participants with MDR-TB and HIV were enrolled and followed up through treatment completion (median 17.2

months interquartile range 12.2-19.6). The median bedaquiline adherence was higher than ART adherence (97 vs. 89%, P < 0.001) but correlated (r2 = 0.68, P < 0.001). High bedaquiline adherence (≥90%) compared with lower adherence was associated with improved end of treatment successful outcome (83.4% vs. 46.3%, P < 0.001), decreased mortality (11.0% vs. 29.6% P = 0.004), and improved retention in care through end of treatment (94.5% vs. 79.6% P = 0.002). Modeling identified a highly significant but linear association between bedaquiline adherence and outcome. On multivariable analysis, bedaquiline adherence was independently associated with mortality and outcome. Bedaquiline resistance-associated variants were seen in 12% (7/57) of sequenced isolates (7% baseline, 5% emergent) with only 28.6% experiencing successful treatment outcome.
CONCLUSIONS: Bedaquiline adherence through 6 months independently predicted end of MDR-TB treatment outcome, but a specific bedaquiline adherence threshold was not identified. Interventions to optimize bedaquiline adherence are urgently needed to improve MDR-TB HIV treatment outcomes.

DOI: 10.1097/QAI.0000000000002940
PMID: 35195572 [Indexed for MEDLINE]

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

39. **Drug re-engineering and repurposing: A significant and rapid approach to tuberculosis drug discovery.**

Arch Pharm (Weinheim). 2022 Jul 15:e2200214. doi: 10.1002/ardp.202200214. Online ahead of print.

Reddy DS(1), Sinha A(1), Kumar A(1), Saini VK(2).

The prevalence of tuberculosis (TB) remains the leading cause of death from a single infectious agent, ranking it above all other contagious diseases. The problem to tackle this disease seems to become even worse due to the outbreak of SARS-CoV-2. Further, the complications related to drug-resistant TB, prolonged treatment regimens, and synergy between TB and HIV are significant drawbacks. There are several drugs to treat TB, but there is still no rapid and accurate treatment available. Intensive research is, therefore, necessary to discover newer molecular analogs that can probably eliminate this disease within a short span. An increase in efficacy can be achieved through re-engineering old TB-drug families and repurposing known drugs. These two approaches have led to the

production of newer classes of compounds with novel mechanisms to treat multidrug-resistant strains. With respect to this context, we discuss structural aspects of developing new anti-TB drugs as well as examine advances in TB drug discovery. It was found that the fluoroquinolone, oxazolidinone, and nitroimidazole classes of compounds have greater potential to be further explored for TB drug development. Most of the TB drug candidates in the clinical phase are modified versions of these classes of compounds. Therefore, here we anticipate that modification or repurposing of these classes of compounds has a higher probability to reach the clinical phase of drug development. The information provided will pave the way for researchers to design and identify newer molecular analogs for TB drug development and also broaden the scope of exploring future-generation potent, yet safer anti-TB drugs.

DOI: 10.1002/ardp.202200214
PMID: 35841594

40. **The global impact of household contact management for children on multidrug-resistant and rifampicin-resistant tuberculosis cases, deaths, and health-system costs in 2019: a modelling study.**

Lancet Glob Health. 2022 Jul;10(7):e1034-e1044. doi: 10.1016/S2214-109X(22)00113-9. Epub 2022 May 18.

Dodd PJ(1), Mafirakureva N(2), Seddon JA(3), McQuaid CF(4).

Comment in
Lancet Glob Health. 2022 Jul;10(7):e942-e943.

BACKGROUND: Estimates suggest that at least 30 000 children develop multidrug-resistant or rifampicin-resistant tuberculosis each year. Despite household contact management (HCM) being widely recommended, it is rarely done. METHODS: We used mathematical modelling to evaluate the potential country-level and global effects and cost-effectiveness of multidrug-resistant or rifampicin-resistant tuberculosis HCM for children younger than 15 years who are living with a person with newly diagnosed multidrug-resistant or rifampicin-resistant tuberculosis. We compared a baseline of no HCM with several HCM strategies and tuberculosis preventive therapy regimens, calculating the effect on multidrug-resistant or rifampicin-resistant tuberculosis cases, deaths, and health-system costs. All HCM strategies involved the screening of children for prevalent tuberculosis disease but with tuberculosis preventive therapy either not given or targeted dependent on age, HIV status, and result of

tuberculin skin test. We evaluated the use of fluoroquinolones (ie, levofloxacin and moxifloxacin), delamanid, and bedaquiline as tuberculosis preventive therapy.
FINDINGS: Compared with a baseline without HCM, HCM for all adults diagnosed with multidrug-resistant or rifampicin-resistant tuberculosis in 2019 would have entailed screening 227 000 children (95% uncertainty interval [UI]: 205 000-252 000) younger than 15 years globally, and averted 2350 tuberculosis deaths (1940-2790), costing an additional US$63 million (74-95 million). If all the children within the household who had been in contact with the person with multidrug-resistant or rifampicin-resistant tuberculosis received tuberculosis preventive therapy with levofloxacin, 5620 incident tuberculosis cases (95% UI 4540-6890) and an additional 1240 deaths (970-1540) would have been prevented. Incremental cost-effectiveness ratios were lower than half of per-capita gross domestic product for most interventions in most countries. Targeting only children younger than 5 years and those living with HIV reduced the number of incident cases and deaths averted, but improved cost-effectiveness. Tuberculosis preventive therapy with delamanid increased the effect, in terms of reduced incidence and mortality, compared with levofloxacin.
INTERPRETATION: HCM for patients with multidrug-resistant or rifampicin-resistant tuberculosis is cost-effective in most settings and could avert a substantial proportion of multidrug-resistant or rifampicin-resistant tuberculosis cases and deaths in children globally.
FUNDING: UK Medical Research Council.

DOI: 10.1016/S2214-109X(22)00113-9
PMCID: PMC9197775
PMID: 35597248 [Indexed for MEDLINE]

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

41. **Comprehensive genomic analysis of Mycobacterium tuberculosis reveals limited impact of high-fitness genotypes on MDR-TB transmission.**

J Infect. 2022 Jul;85(1):49-56. doi: 10.1016/j.jinf.2022.05.012. Epub 2022 May 16.

Chen Y(1), Liu Q(2), Takiff HE(3), Gao Q(4).

OBJECTIVES: Environmental and host-related factors that contribute to the transmission of multidrug-resistant tuberculosis (MDR-TB) have become an increasing concern, but the impact of bacterial genetic factors associated with bacterial fitness on MDR-TB transmission is poorly understood. Here, we present a global view of the correlation between common fitness-related genotypes and MDR-TB transmission by analyzing a representative number of MDR-TB isolates.
METHODS: We assembled a global whole genome sequencing (WGS) dataset of MDR-TB strains collected through retrospective cohorts or population-based approaches using public databases and literature curation. WGS-based clusters were defined as groups of strains with genomic difference of ≤ 5 SNPs.
RESULTS: We curated high-quality WGS data of 4696 MDR-TB isolates from 17 countries with a mean clustering rate of 48% (range 0-100%). Correlational analysis showed that increased risk of MDR-TB strain clustering was not associated with compensatory mutations (OR 1.07, 95% CI 0.72-1.59), low-fitness cost drug-resistant mutations (katG S315T: OR 1.42, 95% CI 0.82-2.47; rpoB S450L: OR 1.26, 95% CI 0.87-1.83) or Lineage 2 (OR 1.50, 95% CI 0.95-2.39).
CONCLUSIONS: The factors most commonly thought to increase bacterial fitness were not significantly associated with increased MDR-TB transmission, and thus do not appear to be major contributors to the current epidemic of MDR-TB.

DOI: 10.1016/j.jinf.2022.05.012
PMID: 35588941 [Indexed for MEDLINE]

Conflict of interest statement: Declaration of Competing Interest None declared.

42. **Novel 2-arylthiazolidin-4-one-thiazole hybrids with potent activity against Mycobacterium tuberculosis.**

Bioorg Chem. 2022 Jul;124:105809. doi: 10.1016/j.bioorg.2022.105809. Epub 2022 Apr 14.

Othman DIA(1), Hamdi A(1), Abdel-Aziz MM(2), Elfeky SM(3).

Substituted aldehydes, ethyl 2-(2-amino-thiazol-4-yl)acetate), and 2-mercaptoacetic acid, in a three-component one-pot green synthetic approach afforded 2-arylthiazolidin-4-one- thiazole hybrids(T1-T13). Compounds showed good anti-tubercular activity towards sensitive M. tuberculosis strain. Compound T8 was as potent as isoniazide (INH) with MIC = 0.12 μg/ml. Compounds T2 and T13 showed potent activity with MIC = 0.48 μg/ml. Other compounds showed moderate to good anti-tubercular activity towards MDR M. tuberculosis strain with MIC range 1.95-125 μg/ml. Compounds T2, T8, T9, and T13 showed anti-tubercular activity

towards XDR M. tuberculosis strain with MIC range 7.81-125 μg/ml. Compounds T2 and T8 were capable of inhibiting M. tuberculosis InhA enzyme in-vitro with IC50 = 1.3 ± 0.61 μM and 1.06 ± 0.97 μM, respectively. Molecular docking simulation showed that T2 and T8 were also capable of interacting at the catalytic site of InhA enzyme in a similar mode to the native ligand through binding with NAD+ and Tyr158. The 3D- QSAR study highlighted the relevance of substitution of phenyl group at position-2 of thiazolidin-4-one where bulky electronegative substitution at position-4 of the phenyl ring favored the activity against M. tuberculosis H37R. Additionally, compounds showed good antibacterial activity against bronchitis causing bacteria M. pneumoniae, S. pneumonia, K. pneumonia, and B. pertussis compared to Azithromycin. In-silico studies of ADMET descriptors and drug-likeness were conducted for all synthesized compounds. Compounds showed good oral bioavailability, good gastrointestinal absorption and showed no signs of adverse effects to the liver or CNS. Compounds showed no potential carcinogenicity as well.

DOI: 10.1016/j.bioorg.2022.105809
PMID: 35447406 [Indexed for MEDLINE]

43. **Recent updates in diagnosis and management of drug-resistant tuberculosis in India: A paradigm shift and the way ahead during the COVID-19 crisis.**

Indian J Tuberc. 2022 Jul;69(3):264-267. doi: 10.1016/j.ijtb.2021.08.013. Epub 2021 Aug 16.

Gupta M(1), Ish P(2), Malhotra N(2).

The recent guidelines on the Programmatic Management of Drug-Resistant Tuberculosis (DR-TB) in India (PMDT) have been released in March 2021 on World TB Day. The new guidelines have considered emerging diagnostic trends including TrueNat, Xpert Mtb/XDR, Next generation sequencing and evaluation for resistance to newer drugs including Bedaquiline (Bdq) and Delamanid. The emerging therapeutic trends include focus on oral shorter Bdq based regimen with phasing out injectables use. The replacement sequence of drugs for DR-TB have also been updated. Updated definitions for pre-XDR, XDR, culture conversion and default have also been added. These guidelines are a paradigm shift which will make treating DR-TB easier and more efficient especially during the ongoing COVID-19 pandemic crisis.

DOI: 10.1016/j.ijtb.2021.08.013
PMCID: PMC8366038
PMID: 35760475 [Indexed for MEDLINE]

Conflict of interest statement: Conflicts of interest The authors have none to declare.

44. **Tapping into the antitubercular potential of 2,5-dimethylpyrroles: A structure-activity relationship interrogation.**

Eur J Med Chem. 2022 Jul 5;237:114404. doi: 10.1016/j.ejmech.2022.114404. Epub 2022 Apr 21.

Semenya D(1), Touitou M(1), Masci D(1), Ribeiro CM(2), Pavan FR(2), Dos Santos Fernandes GF(1), Gianibbi B(3), Manetti F(3), Castagnolo D(4).

An exploration of the chemical space around a 2,5-dimethylpyrrole scaffold of antitubercular hit compound 1 has led to the identification of new derivatives active against Mycobacterium tuberculosis and multidrug-resistant clinical isolates. Analogues incorporating a cyclohexanemethyl group on the methyleneamine side chain at C3 of the pyrrole core, including 5n and 5q, exhibited potent inhibitory effects against the M. tuberculosis strains, substantiating the essentiality of the moiety to their antimycobacterial activity. In addition, selected derivatives showed promising cytotoxicity profiles against human pulmonary fibroblasts and/or murine macrophages, proved to be effective in inhibiting the growth of intracellular mycobacteria, and elicited either bactericidal effects, or bacteriostatic activity comparable to 1. Computational studies revealed that the new compounds bind to the putative target, MmpL3, in a manner similar to that of known inhibitors BM212 and SQ109.

DOI: 10.1016/j.ejmech.2022.114404
PMID: 35486992 [Indexed for MEDLINE]

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

Pharmacol Res. 2022 Jun 30;182:106336. doi: 10.1016/j.phrs.2022.106336. Online ahead of print.

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

46. **Single-Fluorescence ATP Sensor Based on Fluorescence Resonance Energy Transfer Reveals Role of Antibiotic-Induced ATP Perturbation in Mycobacterial Killing.**

mSystems. 2022 Jun 28;7(3):e0020922. doi: 10.1128/msystems.00209-22. Epub 2022 May 26.

Liang L(#)(1)(2), Lin D(#)(1)(2), Chen Y(#)(3), Li J(#)(1)(2), Liang W(1)(2), Zhao H(4), Luo W(3), Tian GB(1)(2), Feng S(1)(2).

The rapid emergence of multidrug-resistant/extensively drug-resistant

tuberculosis (TB) is responsible for treatment failure in patients with TB and significantly endangers global public health. Recently, bioenergetics has become a new paradigm for anti-TB drug discovery and is based on the link between bacterial ATP levels and drug efficacy. A better understanding of the role of ATP fluctuations during antibiotic treatment may provide insight into antibiotic-mediated killing of mycobacteria. Here, we employed an advanced single-fluorescence FRET (fluorescence resonance energy transfer)-based ATP biosensor, ATPser, for the stable and convenient detection of intracellular ATP fluctuations in mycobacteria. This strategy correlated closely with the results obtained from conventional luminescence ATP assays, indicating the reliability of the system for bioenergetics analysis in mycobacteria. Moreover, the reporter strains expressing ATPser displayed obvious ATP changes when subjected to different stresses, such as starvation and ATP depletion. Interestingly, we observed that different antibiotics induced fluctuations in cellular ATP levels in individual cells of various magnitudes, revealing a strong connection between ATP fluctuations and drug efficacy. Furthermore, drug combinations accelerated ATP perturbation, resulting in increased cell death. We concluded that ATPser enabled real-time measurement of ATP at the single-cell level in mycobacteria, and monitoring ATP dynamics in drug-treated bacteria may shed light on novel treatment strategies. IMPORTANCE Bioenergetics has emerged as a new paradigm for antituberculosis (anti-TB) drug discovery, and the cellular ATP level is the core indicator reflecting bacterial metabolic homeostasis. Although several bulk assays have been designed for the measurement of cellular ATP content, a more convenient strategy is required for real-time ATP measurement of single viable cells. In this study, by combining the ε-subunit of Bacillus subtilis FoF1-ATP synthase with a circularly permuted green fluorescent protein [(cp)GFP], we constructed a FRET-based single-fluorescence ATP sensor, ATPser, for real-time single-cell ATP detection among a mycobacterial population. Using the ATPser, we designed different drug combinations containing components that have similar/opposite effects on ATP alternation. Our results demonstrated that increased cellular ATP fluctuations were associated with depletion of mycobacterial viability, while counteracting ATP fluctuations weakened the killing effect of the drug regime. Thus, potentially efficient drug combinations can be considered based on their similar effects on mycobacterial ATP levels, and ATPser may be a useful tool to study mycobacterial bioenergetics and to guide drug regime design.

DOI: 10.1128/msystems.00209-22
PMCID: PMC9238375
PMID: 35615956

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

47. **Being heard on all-oral therapy for resistant tuberculosis.**

Lancet Infect Dis. 2022 Jul;22(7):923-924. doi: 10.1016/S1473-3099(22)00027-5. Epub 2022 May 2.

Furin J(1), Isaakidis P(2).

Comment on
Lancet Infect Dis. 2022 Jul;22(7):1042-1051.

DOI: 10.1016/S1473-3099(22)00027-5
PMID: 35512717 [Indexed for MEDLINE]

Conflict of interest statement: We declare no competing interests.

48. **Global trends, regional differences and age distribution for the incidence of HIV and tuberculosis co-infection from 1990 to 2019: results from the global burden of disease study 2019.**

Infect Dis (Lond). 2022 Jul 7:1-11. doi: 10.1080/23744235.2022.2092647. Online ahead of print.

Wang Y(1), Jing W(1), Liu J(1), Liu M(1).

BACKGROUND: People living with human immunodeficiency virus (HIV) are more likely to develop tuberculosis (TB), and their co-infection (HIV-TB) increases the risk of death. We aimed to describe the global trends, regional differences and age distribution of HIV-TB.
METHODS: Annual new cases, age-standardized incidence rates (ASRs) and age-specific incidence rates with 95% uncertainty intervals (UIs) of HIV-infected drug-susceptible tuberculosis (HIV-DS-TB), HIV-infected multidrug-resistant tuberculosis without extensive drug resistance (HIV-MDR-TB) and HIV-infected extensively drug-resistant tuberculosis (HIV-XDR-TB) during 1990-2019 were collected from the Global Burden of Disease Study 2019. To reveal the trends of HIV-TB by region and age, the percentage change of new cases and estimated annual percentage change (EAPC) of ASRs were calculated.
RESULTS: The ASR of HIV-XDR-TB increased significantly by an average of 14.77% (95% CI: 11.05%-18.62%) per year during 1990-2019 worldwide, while the ASRs of HIV-DS-TB and HIV-MDR-TB decreased after 2005. HIV-XDR-TB was a great threat to Eastern Europe for the largest number of new cases (792, 95% UI: 487-1167) and the highest ASR (0.34 per 100,000 population, 95% UI: 0.21-0.50). In addition, Oceania had the largest rise in ASRs of HIV-MDR-TB (EAPC = 22.56, 95% CI: 18.62-26.64) and HIV-XDR-TB (EAPC = 32.95, 95% CI: 27.90-38.20) during

1990-2019. Recently, age-specific incidence rates of HIV-XDR-TB increased in all age groups, especially in the 50-69 age groups among high, low-middle and low Socio-Demographic Index regions. Additionally, the proportion of patients aged <15 years was nearly 10% of new cases in sub-Saharan Africa in 2019, which was higher than in other regions.
CONCLUSIONS: HIV-infected drug-resistant TB is common in Oceania and Eastern Europe. Moreover, HIV-XDR-TB among elderly people became increasingly prevalent. In the future, the collaboration of management for HIV and TB should be intensified in Oceania and Eastern Europe, and more concerns need to be paid in elderly people.

DOI: 10.1080/23744235.2022.2092647
PMID: 35801264

49. **Non-actionable results, accuracy and effect of the first- and second-line line probe assays for diagnosing drug resistant tuberculosis, including on smear-negative specimens, in a high-volume laboratory.**

Clin Infect Dis. 2022 Jul 5:ciac556. doi: 10.1093/cid/ciac556. Online ahead of print.

Pillay S(1)(2), de Vos M(1), Derendinger B(1), Streicher E(1), Dolby T(2), Scott LA(1), Steinhobel AD(1), Warren RM(1), Theron G(1).

BACKGROUND: Rapid drug susceptibility testing (DST) is crucial to confirm eligibility for new tuberculosis (TB) regimens. Genotype MTBDRsl is a widely-deployed World Health Organization (WHO)-endorsed assay yet programmatic performance data, including non-actionable results from smear-negative sputum, are scarce.
METHODS: Sputa from Xpert MTB/RIF-rifampicin resistant individuals (n=951) were tested by Genotype MTBDRplus and MTBDRsl (both v2) in a routine laboratory. Phenotypic DST was the second-line drug reference standard. Discrepant results underwent Sanger sequencing.
FINDINGS: 89% (849/951) individuals were culture-positive [56% (476/849) smear-negative]. MTBDRplus had at least one non-actionable result (control and/or TB-detection bands absent or invalid, precluding resistance reporting) in 19% (92/476) of smear-negatives and, for MTBDRsl, 40% (171/427) were non-actionable [28% (120/427) false-negative TB, 17% (51/427) indeterminate]. In smear-negatives, MTBDRsl sensitivity for fluoroquinolones was 84% (95% CI 67-93), 81% (54-95) for second-line injectables, and 57% (28-82) for both. Specificities were 93% (89-98), 88% (81-93), and 97% (91-99), respectively. 23% (172/746) of Xpert rifampicin-resistant specimens were MTBDRplus isoniazid-susceptible. Days-to-second-line-susceptibility reporting with the

programmatic advent of MTBDRsl improved [6 (5-7) vs. 37 (35-46); p<0.001]. CONCLUSION: MTBDRsl did not generate a result in almost half of smear-negative individuals (4/10 failed), resulting in substantial missed resistance. However, if MTBDRsl generates an actionable result, that result is accurate in ruling-in second-line resistance. Isoniazid susceptibility testing remains crucial. This study provides, in the context of WHO guidance, real-world direct second-line susceptibility testing performance data on non-actionable results (which, if unaccounted for, result in an overestimation of test utility), accuracy, and care cascade impact.

DOI: 10.1093/cid/ciac556
PMID: 35788278

50. **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.

51. **Molecular detection of isoniazid monoresistance improves tuberculosis treatment: A retrospective cohort in France.**

J Infect. 2022 Jul;85(1):24-30. doi: 10.1016/j.jinf.2022.05.017. Epub 2022 May 20.

Bachir M(1), Guglielmetti L(2), Tunesi S(3), Billard-Pomares T(4), Chiesi S(5), Jaffré J(6), Langris H(7), Pourcher V(8), Schramm F(9), Lemaître N(10), Robert J(2); Isoniazid Resistance Group.

OBJECTIVES: Isoniazid-monoresistant tuberculosis (HR-TB) requires early diagnosis and adapted treatment to achieve optimal outcomes. The primary aim of the study was to assess the impact of the implementation of rapid diagnostic tests on HR-TB treatment in France.
METHODS: We designed a retrospective multicentre study including consecutive HR-TB patients diagnosed in 2016 and 2017. Implementation of a molecular assay detecting isoniazid resistance directly on a clinical sample was recorded. The association between early implementation of such assays and adequate treatment was assessed by a multivariable Cox proportional hazards model.
RESULTS: Overall, 99 HR-TB patients were included from 20 University Hospitals. Among all smear-positive HR-TB patients, only 26% beneficiated from early

molecular HR detection. This detection was independently associated with shorter time to adequate treatment (HR = 2.0 [1.1-3.8], p = 0.03).
CONCLUSION: In our study, molecular detection of HR on an initial sample was independently associated with earlier treatment adaptation.

DOI: 10.1016/j.jinf.2022.05.017
PMID: 35605802 [Indexed for MEDLINE]

Conflict of interest statement: Declaration of Competing Interest None.

52. **Plasma drug concentrations of 4-drug fixed-dose combination regimen and its efficacy for treatment of pulmonary tuberculosis under National Tuberculosis Elimination Programme: A prospective pilot study.**

Indian J Tuberc. 2022 Jul;69(3):311-319. doi: 10.1016/j.ijtb.2021.04.002. Epub 2021 Apr 20.

Bargaje M(1), Bharaswadkar S(2), Lohidasan S(3), Panda BK(4).

BACKGROUND: The thrice weekly dosing regimen of DOTS has shown low rifampicin plasma concentrations as an independent risk factor for unfavourable tuberculosis (TB) outcome. With introduction of daily regimen using fixed dose combinations (FDC) under National Tuberculosis Elimination Programme (NTEP) the existence of suboptimal plasma levels of first-line antitubercular drugs and its clinical significance remain poorly understood.
METHOD: We included a prospective cohort of newly diagnosed pulmonary tuberculosis (PTB) patients receiving 4-FDC daily regimen under NTEP. Plasma concentration at 2 hours (C2h) of each drug was determined after two weeks of treatment using liquid chromatography (LCMS/MS) developed by us. TB card and laboratory reports were reviewed for baseline characteristics and clinical status at 2, 4 and 6 months after the initiation of treatment. At a 1 year follow-up, therapy failure was defined as death or a relapse of tuberculosis.
RESULTS: Among 40 PTB patients, the C2h post dose plasma concentrations of H, R and E were suboptimal in 25%, 60% and 10% respectively. The C2h of H, R, Z and E were respectively 4.2 ± 2.0, 7.3 ± 2.8, 39.2 ± 8.8 and 3.5 ± 1.2 μg/ml; 60% of the patients had suboptimal plasma concentrations and commonly it was observed with H and R. C2h were lower than expected for at least two drugs i.e. H and R in 25% (10/40) of the patients. Plasma concentration of isoniazid and rifampicin has always been considered important for microbiological response and treatment outcome and low concentrations has been associated with poor treatment response. These patients may require a two year follow up and critical evaluation for

prevention of MDR-TB. However, all the TB patients were cured and none of them had recurrence within one year follow up.
CONCLUSIONS: All the pulmonary TB patients administering 4-FDC daily regimen under programmatic settings were cured despite the suboptimal levels of isoniaizd and rifampicin. All the patients achieved pyrazinamide plasma levels and probably this could be the reason behind favourable outcome. Further study is required on large sample size with various subset of population to understand the need of therapeutic drug monitoring.

DOI: 10.1016/j.ijtb.2021.04.002
PMID: 35760480 [Indexed for MEDLINE]

Conflict of interest statement: Conflicts of interest The authors have none to declare.

53. **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]

54. **Factors contributing to the high prevalence of multidrug-resistance/Rifampicin-resistance in patients with tuberculosis: an epidemiological cross sectional and qualitative study from Khabarovsk krai region of Russia.**

BMC Infect Dis. 2022 Jul 13;22(1):612. doi: 10.1186/s12879-022-07598-7.

Bykov I(1)(2), Dyachenko O(3), Ratmanov P(2), Liu H(1), Liang L(1), Wu Q(4).

BACKGROUND: Growing prevalence of multidrug-resistant/Rifampicin-resistant tuberculosis (MDR/RR-TB; resistance to Isoniazid and Rifampicin/Isolated resistance to Rifampicin) is putting in jeopardy the WHO End TB strategy. This study aimed to identify factors contributing to the high prevalence of MDR/RR-TB in Khabarovsk krai region of Russia.
METHODS: A cross-sectional retrospective study was conducted, analyzing clinical, demographic, and drug susceptibility testing data on 1440 patients. As a source of raw data, the national electronic TB surveillance system was used. Anonymous data was collected on every patient diagnosed with TB in all healthcare facilities of the region from January 2018 to December 2019. Only patients with proven excretion of m. tuberculosis were included in the study. Factors associated with MDR/RR-TB were identified through logistic regression analysis, in conjunction with in-depth interviews with eight patients, five healthcare managers and five doctors.

FINDINGS: 2661 patients were identified with TB, 1440 were incorporated in the study based on inclusion criteria. Of these, 618 (42.9%) were identified with MDR/RR-TB. Patients with a history of imprisonment were 16.53 times (95% CI 5.37 to 50.88,) more likely to have MDR/RR-TB, whereas re-treatment patients were 2.82 times (95% CI 2.16 to 3.66) more likely to have MDR/RR-TB. Other influencing factors included presence of disability (AOR is 2.32, 95% CI 1.38 to 3.89), cavitary disease (AOR is 1.76, 95% CI 1.37 to 2.25), and retirement status (AOR 0.65, 95% CI 0.43 to 0.98, p = 0.042). Poor patient knowledge and understanding of the disease, progressive weariness of prolonged TB treatment, and inability hospitalize infectious patients without their consent were perceived by the interviewees as major influencing factors.
CONCLUSIONS: Incarceration and treatment history, regardless of outcome, were identified as major factors influencing MDR/RR-TB prevalence. It is essential for the TB care system to eliminate legal loopholes, which deprive doctors of means to enforce quarantine procedures and epidemiological surveillance on infected patients, former and current inmates. Increasing people's awareness of TB, early detection and appropriate treatment of patients with TB are needed for successfully combating MDR/RR-TB.

DOI: 10.1186/s12879-022-07598-7
PMCID: PMC9281178
PMID: 35831812 [Indexed for MEDLINE]

Conflict of interest statement: None declared.

55. **Treatment outcomes 24 months after initiating short, all-oral bedaquiline-containing or injectable-containing rifampicin-resistant tuberculosis treatment regimens in South Africa: a retrospective cohort study.**

Lancet Infect Dis. 2022 Jul;22(7):1042-1051. doi: 10.1016/S1473-3099(21)00811-2. Epub 2022 May 2.

Ndjeka N(1), Campbell JR(2), Meintjes G(3), Maartens G(3), Schaaf HS(4), Hughes J(4), Padanilam X(5), Reuter A(6), Romero R(7), Ismail F(8), Enwerem M(9), Ferreira H(10), Conradie F(11), Naidoo K(12), Menzies D(2).

Comment in
Lancet Infect Dis. 2022 Jul;22(7):923-924.

BACKGROUND: There is a need for short and safe all-oral treatment of rifampicin-resistant tuberculosis. We compared outcomes up to 24 months after

treatment initiation for patients with rifampicin-resistant tuberculosis in South Africa treated with a short, all-oral bedaquiline-containing regimen (bedaquiline group), or a short, injectable-containing regimen (injectable group).
METHODS: Patients with rifampicin-resistant tuberculosis, aged 18 years or older, eligible for a short regimen starting treatment between Jan 1 and Dec 31, 2017, with a bedaquiline-containing or WHO recommended injectable-containing treatment regimen of 9-12 months, registered in the drug-resistant tuberculosis database (EDRWeb), and with known age, sex, HIV status, and national identification number were eligible for study inclusion; patients receiving linezolid, carbapenems, terizidone or cycloserine, delamanid, or para-aminosalicylic acid were excluded. Bedaquiline was given at a dose of 400 mg once daily for two weeks followed by 200 mg three times a week for 22 weeks. To compare regimens, patients were exactly matched on HIV and ART status, previous tuberculosis treatment history, and baseline acid-fast bacilli smear and culture result, while propensity score matched on age, sex, province of treatment, and isoniazid-susceptibility status. We did binomial linear regression to estimate adjusted risk differences (aRD) and 95% CIs for 24-month outcomes, which included: treatment success (ie, cure or treatment completion without evidence of recurrence) versus all other outcomes, survival versus death, disease free survival versus survival with treatment failure or recurrence, and loss to follow-up versus all other outcomes.
FINDINGS: Overall, 1387 (14%) of 10152 patients with rifampicin-resistant tuberculosis treated during 2017 met inclusion criteria; 688 in the bedaquiline group and 699 in the injectable group. Four patients (1%) had treatment failure or recurrence, 44 (6%) were lost to follow-up, and 162 (24%) died in the bedaquiline group, compared with 17 (2%), 87 (12%), and 199 (28%), respectively, in the injectable group. In adjusted analyses, treatment success was 14% (95% CI 8-20) higher in the bedaquiline group than in the injectable group (70% vs 57%); loss to follow-up was 4% (1-8) lower in the bedaquiline group (6% vs 12%); and disease-free survival was 2% (0-5) higher in the bedaquiline group (99% vs 97%). The bedaquiline group had 8% (4-11) lower risk of mortality during treatment (17·0% vs 22·4%), but there was no difference in mortality post-treatment.
INTERPRETATION: Patients in the bedaquiline group experienced significantly higher rates of treatment success at 24 months. This finding supports the use of short bedaquiline-containing regimens in eligible patients.
FUNDING: WHO Global TB Programme.
TRANSLATION: For the French translation of the abstract see Supplementary Materials section.

DOI: 10.1016/S1473-3099(21)00811-2
PMCID: PMC9217754
PMID: 35512718 [Indexed for MEDLINE]

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

56. **Clinical standards for drug-susceptible TB: putting patients first.**

Int J Tuberc Lung Dis. 2022 Jul 1;26(7):584-586. doi: 10.5588/ijtld.22.0240.

van der Werf TS(1), Grobusch MP(2).

DOI: 10.5588/ijtld.22.0240
PMID: 35768922 [Indexed for MEDLINE]

57. **Detection and characterization of mutations in genes related to isoniazid resistance in Mycobacterium tuberculosis clinical isolates from Iran.**

Mol Biol Rep. 2022 Jul;49(7):6135-6143. doi: 10.1007/s11033-022-07404-2. Epub 2022 Apr 2.

Bakhtiyariniya P(1)(2), Khosravi AD(3)(4)(5), Hashemzadeh M(1)(2), Savari M(1)(2).

BACKGROUND: The global rise in drug-resistant Mycobacterium tuberculosis (M.tb), and especially the significant prevalence of isoniazid (INH)-resistance constitute a significant challenge to global health. Therefore, the present study aimed to investigate mutations in prevalent gene loci-involved in INH-resistance phenotype-among M.tb clinical isolates from southwestern Iran.
METHODS: Drug susceptibility testing (DST) was performed using the conventional proportional method on confirmed 6620 M.tb clinical isolates, and in total, 15 INH-resistant and 18 INH-susceptible isolates were included in the study. Fragments of six genetic loci most related to INH-resistance (katG, inhA promoter, furA, kasA, ndh, oxyR-ahpC intergenic region) were PCR-amplified and sequenced. Mutations were explored by pairwise alignment with the M.tb H37Rv genome.
RESULTS: The analysis of gene loci revealed 13 distinct mutations in INH-resistant isolates. 60% (n = 9) of the INH-resistant isolates had mutations

in katG, with codon 315 predominately (53.3%, n = 8). Mutation at InhA - 15 was found in 20% (n = 3) of resistant isolates. 26.7% (n = 4) of the INH-resistant isolates had kasA mutations, of which G269S substitution was the most common (20%, n = 3). The percentage of mutations in furA, oxyR-ahpC and ndh was 6.7% (n = 1), 46.7% (n = 7), and 20% (n = 3), respectively. Of the mutations detected in ndh and oxyR-ahpC, 5 were also observed in INH-susceptible isolates. This study revealed seven novel mutations, four of which were exclusively in resistant isolates.
CONCLUSIONS: This study supports the usefulness of katG and inhA mutations as a predictive molecular marker for INH resistance. Co-detection of katG S315 and inhA-15 mutations identified 73.3% (11 out of 15 isolates) of INH-resistant isolates.

DOI: 10.1007/s11033-022-07404-2
PMCID: PMC8976162
PMID: 35366177 [Indexed for MEDLINE]

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

58. **Knowledge, attitudes and practices of community treatment supporters administering multidrug-resistant tuberculosis injections: A cross-sectional study in rural Eswatini.**

PLoS One. 2022 Jul 14;17(7):e0271362. doi: 10.1371/journal.pone.0271362. eCollection 2022.

Peresu E(1), Heunis JC(2), Kigozi NG(2), De Graeve D(3).

BACKGROUND: This study assessed knowledge, attitudes and practices (KAP) of lay community treatment supporters (CTSs) delegated with directly observed treatment (DOT) supervision and administration of intramuscular multidrug-resistant tuberculosis (MDR-TB) injections in the Shiselweni region in Eswatini.
METHODOLOGY: A cross-sectional survey among a purposive sample of 82 CTSs providing DOT and administering injections to MDR-TB patients was conducted in May 2017. Observations in the patients' homes were undertaken to verify CTSs' self-reported community-based MDR-TB management practices.
RESULTS: Out of 82 respondents, 78 (95.1%) were female and half (n = 41; 50.0%) had primary education or lower. Over one-tenth (n = 12; 14.6%) had not attended a MDR-TB training workshop, but were administering injections. The overall KAP scores were satisfactory. Good self-reported community-based MDR-TB practices were largely verified through observation. However, substantial proportions of

respondents incorrectly defined MDR-TB, were unaware of the treatment regimen, stigmatised patients, and underreported needlestick injuries. There was no statistically significant association between duration administering intramuscular injections, MDR-TB training, knowledge and attitudes, and good community-based MDR-TB management practices.
CONCLUSIONS: The gaps in the current KAP of CTSs in this setting raise questions about the timing, adequacy, design and content of community-based MDR-TB management training. Nonetheless, with appropriate training, lay CTSs in this region can be an option to complement an overstretched professional health workforce in providing DOT and MDR-TB injections at community level.

DOI: 10.1371/journal.pone.0271362
PMCID: PMC9282659
PMID: 35834492 [Indexed for MEDLINE]

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

59. **Corrigendum to 'Culture conversion at six months in patients receiving bedaquiline- and delamanid-containing regimens for the treatment of multidrug-resistant tuberculosis' International Journal of Infectious Diseases Volume 113S1 (2021) S91-S95.**

Int J Infect Dis. 2022 Aug;121:105. doi: 10.1016/j.ijid.2022.05.004. Epub 2022 May 23.

Maretbayeva SM(1), Rakisheva AS(2), Adenov MM(3), Yeraliyeva LT(3), Algozhin YZ(1), Stambekova AT(1), Berikova EA(3), Yedilbayev A(4), Rich ML(5), Seung KJ(5), Issayeva AM(6).

Erratum for
Int J Infect Dis. 2021 Dec;113 Suppl 1:S91-S95.

DOI: 10.1016/j.ijid.2022.05.004
PMID: 35613479

60. **Intra-host genetic population diversity: Role in emergence and persistence of drug resistance among Mycobacterium tuberculosis complex minor variants.**

Infect Genet Evol. 2022 Jul;101:105288. doi: 10.1016/j.meegid.2022.105288. Epub 2022 Apr 27.

Vázquez-Chacón CA(1), de Jesús Rodríguez-Gaxiola F(2), Sánchez-Flores A(3), Montaño S(2), Bello-Rios C(4), Fonseca-Coronado S(5), López-Carrera CF(6), Martínez-Guarneros A(7), Parra-Unda R(2), García-Magallanes N(8), Arámbula-Meraz E(2), Escobar-Gutiérrez A(7), Cruz-Rivera M(9), López-Durán PA(10).

Drug resistant tuberculosis (DR-TB) is an important public health issue in different parts of the world. Mycobacterium tuberculosis complex variants (MTBC vars) preferentially infect certain hosts, limiting their distribution to different ecosystems. However, MTBC vars can infect other hosts beyond their preferred target potentially contributing to persistence of drug resistance (DR) in other niches. Here, we performed a comprehensive intra-host genetic analysis for the identification of DR-related mutations among all MTBC minor vars whole genome sequences (8,095 strains) publicly available worldwide. High confidence drug-resistance mutations in katG (isoniazid), rpsL (streptomycin), pncA (pyrazinamide), rpoB (rifampicin) and gyrA (fluoroquinolones) genes were identified among intrahost minor sub-populations in 197 different strains (2.43%) belonging to vars africanum, bovis, caprae, microti, orygis and pinnipedii. In addition, a three-dimensional structure modeling analysis to assess the role of novel mutations was also performed. Our findings highlight the importance of detecting discrete intra-host populations carrying DR mutations.

DOI: 10.1016/j.meegid.2022.105288
PMID: 35489699 [Indexed for MEDLINE]

61. **In vitro activity of tedizolid and linezolid against multidrug-resistant Mycobacterium tuberculosis: a comparative study using microdilution broth assay and genomics.**

Diagn Microbiol Infect Dis. 2022 Jul;103(3):115714. doi: 10.1016/j.diagmicrobio.2022.115714. Epub 2022 Apr 22.

Aono A(1), Murase Y(2), Chikamatsu K(2), Igarashi Y(2), Shimomura Y(2), Hosoya M(2), Osugi A(2), Morishige Y(2), Takaki A(2), Yamada H(2), Mitarai S(3).

The effects of tedizolid (TZD) against multidrug-resistant Mycobacterium tuberculosis isolates were investigated. This is possibly the first study to evaluate the MIC of TZD against Japanese Mycobacterium tuberculosis isolates. As TZD had a significantly lower MIC than LZD ($P < 0.01$), it was suggested to be a better, non-toxic alternative to LZD.

DOI: 10.1016/j.diagmicrobio.2022.115714
PMID: 35596983 [Indexed for MEDLINE]

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

62. **Assessment of the Carcinogenic Potential of Pretomanid in Transgenic Tg.rasH2 Mice.**

Int J Toxicol. 2022 Jul 18:10915818221113295. doi: 10.1177/10915818221113295. Online ahead of print.

Ambroso JL(1), Dillberger J(2), Bruning-Barry R(1), Yang T(3).

Pretomanid is a nitroimidazooxazine antimycobacterial drug that was approved as part of a three-drug oral regimen, consisting of bedaquiline, pretomanid, and linezolid, for 6-months treatment of adults with pulmonary extensively drug-resistant tuberculosis or with complicated forms of multidrug-resistant tuberculosis by the food and drug administration in the United States and regulatory bodies in over 10 other countries. Nitroaromatic compounds as a class carry a risk of genotoxicity and potential carcinogenicity based on reactive metabolite formation. A battery of good laboratory practice genotoxicity studies on pretomanid indicated that the compound was not genotoxic, however its hydroxy imidazole metabolite (M50) was genotoxic in the Ames assay. To assess the in vivo carcinogenic potential of pretomanid, hemizygous Tg.rasH2 mice were administered pretomanid once daily by oral gavage for 26 weeks. Male mice were given pretomanid in vehicle at doses of 0, 5, 15 and 40 mg/kg/day and female mice were given pretomanid in vehicle at doses of 0, 10, 30 and 80 mg/kg/day. Positive control mice of both sexes received intraperitoneal injections of urethane at 1000 mg/kg on Days 1, 3 and 5. There were no pretomanid-related early deaths, tumors, non-neoplastic microscopic findings, or gross necropsy findings at any dose level. The positive control gave the anticipated response of lung tumors. Oral administration of pretomanid to mice produced plasma exposure to the parent compound (high dose AUC of pretomanid 3 times the clinical AUC at the maximum recommended human dose) and exposure to the M50 metabolite (less than 10% of pretomanid) at all dose levels in both sexes. These data show that pretomanid was not carcinogenic in a transgenic mouse model at systemic exposures greater than human therapeutic exposures.

DOI: 10.1177/10915818221113295
PMID: 35849539

63. **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]

64. **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.

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PMID: 35577251 [Indexed for MEDLINE]

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

65. **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]

66. **Chemical Exploration of a Highly Selective Scaffold with Activity against Intracellular Mycobacterium tuberculosis.**

Microbiol Spectr. 2022 Jun 29;10(3):e0116122. doi: 10.1128/spectrum.01161-22. Epub 2022 May 25.

Njikan S(1)(2), Ahmed S(1)(2), Manning A(1), Awasthi D(1), Ovechkina Y(1)(2), Chowdhury S(1)(2), Butts A(1)(2), Parish T(1)(2).

We previously identified a phenylthiourea series with activity against intracellular Mycobacterium tuberculosis using a high-throughput, high-content assay. We conducted a catalog structure-activity relationship study with a collection of 35 analogs. We identified several thiourea derivatives with excellent potency against intracellular bacteria and good selectivity over eukaryotic cells. Compounds had much lower activity against extracellular bacteria, which was not increased by using cholesterol as the sole carbon source. Compounds were equally active against strains with mutations in QcrB or MmpL3, thereby excluding common, promiscuous targets as the mode of action. The phenylthiourea series represents a good starting point for further exploration to develop novel antitubercular agents. IMPORTANCE Mycobacterium tuberculosis is responsible for the highest number of deaths from a bacterial pathogen, with

>1.5 million in 2020. M. tuberculosis is a sophisticated pathogen that can replicate inside immune cells. There is an urgent need for new drugs to combat M. tuberculosis and to shorten therapy from 6 to 24 months. We have identified a series of molecules that inhibit the growth of M. tuberculosis inside macrophages; we tested a number of derivatives to link structural features to biological activity. The compounds are likely to have novel mechanism of action and so could be developed as new agents for drug-resistant tuberculosis.

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PMCID: PMC9241686
PMID: 35612308 [Indexed for MEDLINE]

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

67. **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.

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PMCID: PMC8786254
PMID: 34935599 [Indexed for MEDLINE]

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

68. **Is body height a prognostic marker for outcome of tuberculosis treatment?**

Infect Dis (Lond). 2022 Jul;54(7):538-541. doi: 10.1080/23744235.2022.2047777. Epub 2022 Mar 14.

Bach F(1), Wejse C(1)(2)(3), Storgaard M(2)(3), Patsche CB(1)(4).

DOI: 10.1080/23744235.2022.2047777
PMID: 35285382 [Indexed for MEDLINE]

69. **Are we ready with fluroquinolone based treatment regimen for drug resistance tuberculosis in a resource limited country?**

Indian J Tuberc. 2022 Jul;69(3):374-375. doi: 10.1016/j.ijtb.2022.04.005. Epub 2022 Apr 29.

Rai DK(1), Sharma P(2).

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PMID: 35760492 [Indexed for MEDLINE]

Conflict of interest statement: Conflicts of interest The authors have none to declare.

70. **Treatment adherence status of the TB patients notified from private sector and its associated factors: Findings of a secondary data analysis from West Bengal, India.**

Indian J Tuberc. 2022 Jul;69(3):334-340. doi: 10.1016/j.ijtb.2021.06.001. Epub 2021 Jun 16.

Dey A(1), Lahiri A(2), Jha SS(3), Sharma V(4), Shanmugam P(4), Chakrabartty AK(5).

INTRODUCTION: In India, each year, estimated one million TB cases are missing from notification, most of them being diagnosed treated in private sector. The large number of patients in private sector has raised concerns about suboptimal quality of care; lack of systems for treatment adherence thus raising the risk of drug resistance. The current analysis was conducted to find out the status of TB treatment adherence in private sector & to identify the factors associated with poor TB treatment adherence.
METHODS: Analysis of secondary data obtained through adherence monitoring house visit by THALI (an USAID funded project) field workers during July 2018-June 2019, was done.
RESULTS: Default rate among the private patients was 5%. Among the private TB patients 81.6% & among the defaulter 87.3% were in the age bracket of 15-59 years. Reasons stated for being a defaulter were 'Medicine is not working' (30%), 'Travel' (28.6%), 'Cost involved in the treatment' (21.8%), 'Side effects of ATD' (11.6%), 'Anxiety or Depression' (7.2%) & 'Feeling of completely cured' (0.8%). Despite best of efforts only 36.9% defaulter could be retrieved. Factors associated with increased risk of lost to follow-up were 15-59 years age, male sex, earning member of the family,tobacco user, alcohol user, DR-TB, continuation phase of treatment, previous history of TB, presence of symptoms & inability to walk.
CONCLUSION: Privately treated TB patients are vulnerable for non-adherence. Once defaulted, it is difficult to retrieve them. Economically productive age group is at higher risk of being defaulter. Commonest reason for lost to follow up is wrong impression about TB medicine. Program should think of extensive engagement & sensitization drive for the private providers; Strict adherence monitoring of private TB patients, extensive advocacy communication & social mobilization program in the community & workplaces/institutions.

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PMID: 35760483 [Indexed for MEDLINE]

Conflict of interest statement: Conflicts of interest The authors have none to declare.

71. **Variants in Bedaquiline-Candidate-Resistance Genes: Prevalence in Bedaquiline-Naive Patients, Effect on MIC, and Association with Mycobacterium tuberculosis Lineage.**

Antimicrob Agents Chemother. 2022 Jun 27:e0032222. doi: 10.1128/aac.00322-22. Online ahead of print.

Rivière E(1)(2), Verboven L(1)(2), Dippenaar A(1), Goossens S(1)(2), De Vos E(1), Streicher E(3), Cuypers B(2)(4), Laukens K(2), Ben-Rached F(5), Rodwell TC(6)(7), Pain A(5)(8), Warren RM(3), Heupink TH(1), Van Rie A(1).

Studies have shown that variants in bedaquiline-resistance genes can occur in isolates from bedaquiline-naive patients. We assessed the prevalence of variants in all bedaquiline-candidate-resistance genes in bedaquiline-naive patients, investigated the association between these variants and lineage, and the effect on phenotype. We used whole-genome sequencing to identify variants in bedaquiline-resistance genes in isolates from 509 bedaquiline treatment naive South African tuberculosis patients. A phylogenetic tree was constructed to investigate the association with the isolate lineage background. Bedaquiline MIC was determined using the UKMYC6 microtiter assay. Variants were identified in 502 of 509 isolates (98.6%), with the highest (85%) prevalence of variants in the Rv0676c (mmpL5) gene. We identified 36 unique variants, including 19 variants not reported previously. Only four isolates had a bedaquiline MIC equal to or above the epidemiological cut-off value of 0.25 μg/mL. Phylogenetic analysis showed that 14 of the 15 variants observed more than once occurred monophyletically in one Mycobacterium tuberculosis (sub)lineage. The bedaquiline MIC differed between isolates belonging to lineage 2 and 4 (Fisher's exact test, P = 0.0004). The prevalence of variants in bedaquiline-resistance genes in isolates from bedaquiline-naive patients is high, but very few (<2%) isolates were phenotypically resistant. We found an association between variants in bedaquiline resistance genes and Mycobacterium tuberculosis (sub)lineage, resulting in a lineage-dependent difference in bedaquiline phenotype. Future studies should investigate the impact of the presence of variants on bedaquiline-resistance acquisition and treatment outcome.

DOI: 10.1128/aac.00322-22
PMID: 35758754

72. **Pharmacokinetics and Safety of WHO-recommended Dosage and Higher Dosage of Levofloxacin for Tuberculosis Treatment in Children: A pilot study.**

Int J Infect Dis. 2022 Jul 13:S1201-9712(22)00425-8. doi: 10.1016/j.ijid.2022.07.029. Online ahead of print.

Jantarabenjakul W(1), Suntarattiwong P(2), Wacharachaisurapol N(3), Ayudhya PSN(2), Phaisal W(4), Tawan M(5), Moonwong J(5), Sudjaritruk T(6), Chariyavilaskul P(4), Puthanakit T(7).

OBJECTIVES: To evaluate the pharmacokinetic (PK) parameters of the 2020 WHO-recommended pediatric dosage of levofloxacin and a higher than WHO dosage.
METHODS: Children aged 1 to 15 years old with tuberculosis who received levofloxacin-based treatment for at least seven days were enrolled. Firstly, five children were enrolled to receive the WHO-recommended dosage (15-20 mg/kg/day) then an additional five children received a higher than WHO dosage (20-30 mg/kg/day). Blood samples were collected at pre-dose and post-dose 1, 2, 4, 6, 8, and 12 hours. A target of the ratio of the free area under the concentration-time curve to minimum inhibitory concentration ratio (fAUC/MIC) was 100.
RESULTS: The median (IQR) age was 9.6 (4.9-10.5) and 12.0 (10.1-12.3) years old in the WHO dosage and the higher than WHO dosage groups, respectively. The median (IQR) duration of anti-TB treatment was 24 (8-24) weeks. The geometric mean (95% confidence interval, 95%CI) of fAUC/MIC was 60.4 (43.5-84.0) and 103.2 (70.1-151.8) in the WHO- and higher than WHO dosage groups, respectively. There was no adverse event of QT prolongation or any other grade 3 or 4 adverse events.
CONCLUSIONS: Levofloxacin at higher dose of 20-30 mg/kg/day could achieve the fAUC/MIC target in children.

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PMID: 35842213