February Literature

1. **Prevalence of multidrug-resistant tuberculosis in prisons: Systematic review and meta-analysis.**

Indian J Med Microbiol. 2022 Feb 1:S0255-0857(22)00004-4. doi: 10.1016/j.ijmmb.2022.01.004. Online ahead of print.

Moreira TR(1), Passos IBJ(2), Bueno JVL(3), Maffacciolli R(4), Colodette RM(5), Miguel PS(6).

BACKGROUND: In the context of prisons, multidrug-resistant tuberculosis (MDR-TB) is a major problem. In this article, we estimate the prevalence of MDR-TB among the population deprived of freedom from countries in South America, Europe, Asia and Africa.
METHODS: The articles were retrieved through systematic search at four databases (EMBASE, CINAHL, LILACS and MEDILINE). The meta-analysis was developed by the random effect model, using the Mantel-Haenszel method, with presentation of the aggregated results through the forest plot. The degree of heterogeneity between the studies was verified using Cochran's Q test and I2.
RESULTS: Of the 102 articles analyzed, 21 were included in this systematic review. The analysis showed heterogeneity indicated by the Q test ($P < 0.001$) and I2 statistics (I2 = 50.52%). The funnel graph and Egger test ($P < 0.830$) showed symmetry between investigations. The grouped prevalence of MDR-TB was 0.48% (95% CI: 0.02 to 1.32), advancing to 1.15 (95% CI: 0.15 to 2.73) when culture and sensitivity test were considered by the authors. No specific characteristics were significantly associated with differences in prevalence rates in the population deprived of freedom.
CONCLUSION: The study reaffirms the magnitude of MDR-TB in the population deprived of freedom in the world context. Political and technical-scientific efforts should be mobilized to mitigate TB and MDR-TB in prisons and for successful national and international disease control programs.

DOI: 10.1016/j.ijmmb.2022.01.004
PMID: 35120789

2. **Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis.**

Lancet. 2022 Feb 12;399(10325):629-655. doi: 10.1016/S0140-6736(21)02724-0. Epub 2022 Jan 19.

Antimicrobial Resistance Collaborators.

Collaborators: Murray CJ, Ikuta KS, Sharara F, Swetschinski L, Robles Aguilar G, Gray A, Han C, Bisignano C, Rao P, Wool E, Johnson SC, Browne AJ, Chipeta MG, Fell F, Hackett S, Haines-Woodhouse G, Kashef Hamadani BH, Kumaran EAP, McManigal B, Agarwal R, Akech S, Albertson S, Amuasi J, Andrews J, Aravkin A, Ashley E, Bailey F, Baker S, Basnyat B, Bekker A, Bender R, Bethou A, Bielicki J, Boonkasidecha S, Bukosia J, Carvalheiro C, Castañeda-Orjuela C, Chansamouth V, Chaurasia S, Chiurchiù S, Chowdhury F, Cook AJ, Cooper B, Cressey TR, Criollo-Mora E, Cunningham M, Darboe S, Day NPJ, De Luca M, Dokova K, Dramowski A, Dunachie SJ, Eckmanns T, Eibach D, Emami A, Feasey N, Fisher-Pearson N, Forrest K, Garrett D, Gastmeier P, Giref AZ, Greer RC, Gupta V, Haller S, Haselbeck A, Hay SI, Holm M, Hopkins S, Iregbu KC, Jacobs J, Jarovsky D, Javanmardi F, Khorana M, Kissoon N, Kobeissi E, Kostyanev T, Krapp F, Krumkamp R, Kumar A, Kyu HH, Lim C, Limmathurotsakul D, Loftus MJ, Lunn M, Ma J, Mturi N, Munera-Huertas T, Musicha P, Mussi-Pinhata MM, Nakamura T, Nanavati R, Nangia S, Newton P, Ngoun C, Novotney A, Nwakanma D, Obiero CW, Olivas-Martinez A, Olliaro P, Ooko E, Ortiz-Brizuela E, Peleg AY, Perrone C, Plakkal N, Ponce-de-Leon A, Raad M, Ramdin T, Riddell A, Roberts T, Robotham JV, Roca A, Rudd KE, Russell N, Schnall J, Scott JAG, Shivamallappa M, Sifuentes-Osornio J, Steenkeste N, Stewardson AJ, Stoeva T, Tasak N, Thaiprakong A, Thwaites G, Turner C, Turner P, van Doorn HR, Velaphi S, Vongpradith A, Vu H, Walsh T, Waner S, Wangrangsimakul T, Wozniak T, Zheng P, Sartorius B, Lopez AD, Stergachis A, Moore C, Dolecek C, Naghavi M.

BACKGROUND: Antimicrobial resistance (AMR) poses a major threat to human health around the world. Previous publications have estimated the effect of AMR on incidence, deaths, hospital length of stay, and health-care costs for specific pathogen-drug combinations in select locations. To our knowledge, this study presents the most comprehensive estimates of AMR burden to date.
METHODS: We estimated deaths and disability-adjusted life-years (DALYs) attributable to and associated with bacterial AMR for 23 pathogens and 88 pathogen-drug combinations in 204 countries and territories in 2019. We obtained data from systematic literature reviews, hospital systems, surveillance systems, and other sources, covering 471 million individual records or isolates and 7585 study-location-years. We used predictive statistical modelling to produce estimates of AMR burden for all locations, including for locations with no data. Our approach can be divided into five broad components: number of deaths where infection played a role, proportion of infectious deaths attributable to a given infectious syndrome, proportion of infectious syndrome deaths attributable to a given pathogen, the percentage of a given pathogen resistant to an antibiotic of

interest, and the excess risk of death or duration of an infection associated with this resistance. Using these components, we estimated disease burden based on two counterfactuals: deaths attributable to AMR (based on an alternative scenario in which all drug-resistant infections were replaced by drug-susceptible infections), and deaths associated with AMR (based on an alternative scenario in which all drug-resistant infections were replaced by no infection). We generated 95% uncertainty intervals (UIs) for final estimates as the 25th and 975th ordered values across 1000 posterior draws, and models were cross-validated for out-of-sample predictive validity. We present final estimates aggregated to the global and regional level.

FINDINGS: On the basis of our predictive statistical models, there were an estimated 4·95 million (3·62-6·57) deaths associated with bacterial AMR in 2019, including 1·27 million (95% UI 0·911-1·71) deaths attributable to bacterial AMR. At the regional level, we estimated the all-age death rate attributable to resistance to be highest in western sub-Saharan Africa, at 27·3 deaths per 100 000 (20·9-35·3), and lowest in Australasia, at 6·5 deaths (4·3-9·4) per 100 000. Lower respiratory infections accounted for more than 1·5 million deaths associated with resistance in 2019, making it the most burdensome infectious syndrome. The six leading pathogens for deaths associated with resistance (Escherichia coli, followed by Staphylococcus aureus, Klebsiella pneumoniae, Streptococcus pneumoniae, Acinetobacter baumannii, and Pseudomonas aeruginosa) were responsible for 929 000 (660 000-1 270 000) deaths attributable to AMR and 3·57 million (2·62-4·78) deaths associated with AMR in 2019. One pathogen-drug combination, meticillin-resistant S aureus, caused more than 100 000 deaths attributable to AMR in 2019, while six more each caused 50 000-100 000 deaths: multidrug-resistant excluding extensively drug-resistant tuberculosis, third-generation cephalosporin-resistant E coli, carbapenem-resistant A baumannii, fluoroquinolone-resistant E coli, carbapenem-resistant K pneumoniae, and third-generation cephalosporin-resistant K pneumoniae.

INTERPRETATION: To our knowledge, this study provides the first comprehensive assessment of the global burden of AMR, as well as an evaluation of the availability of data. AMR is a leading cause of death around the world, with the highest burdens in low-resource settings. Understanding the burden of AMR and the leading pathogen-drug combinations contributing to it is crucial to making informed and location-specific policy decisions, particularly about infection prevention and control programmes, access to essential antibiotics, and research and development of new vaccines and antibiotics. There are serious data gaps in many low-income settings, emphasising the need to expand microbiology laboratory capacity and data collection systems to improve our understanding of this important human health threat.

FUNDING: Bill & Melinda Gates Foundation, Wellcome Trust, and Department of Health and Social Care using UK aid funding managed by the Fleming Fund.

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PMID: 35065702

3. **Tuberculosis of the spine and drug resistance: a review article.**

Neurosurg Rev. 2022 Feb;45(1):217-229. doi: 10.1007/s10143-021-01595-1. Epub 2021 Jun 26.

Kumar V(1), Neradi D(1), Sherry B(1), Gaurav A(1), Dhatt SS(2).

Pott's spine is tuberculosis of spine caused due to hematogenous spread of mycobacterium from a primary focus. It constitutes about 50% of skeletal tuberculosis cases. Paradiscal type is the most common type of spinal tuberculosis. Untreated cases can lead to complications like a cold abscess, paraplegia, and deformity which may require surgical intervention. Rapid molecular methods have made the diagnosis of spinal tuberculosis and drug resistance faster and easier but it still remains a problem due to difficulties in sample collection and the paucibacillary nature of the Pott spine. Antitubercular drug therapy forms the mainstay of management. The emergence of MDR TB and XDR TB has posed a big challenge in the management of spinal tuberculosis. The literature regarding drug resistance in spinal tuberculosis and its management is lacking. We conducted a literature review of 29 studies and presented information on pathogenesis, diagnosis, and management of spinal tuberculosis and drug resistance. New shorter regimens for MDR and XDR TB are under trial in different parts of the world. We believe this article will provide information on spinal tuberculosis and drug resistance and help clinicians outline important research areas.

DOI: 10.1007/s10143-021-01595-1
PMID: 34176000 [Indexed for MEDLINE]

4. **Population Pharmacokinetic and Concentration-QTc Analysis of Delamanid in Pediatric Participants with Multidrug-Resistant Tuberculosis.**

Antimicrob Agents Chemother. 2022 Feb 15;66(2):e0160821. doi: 10.1128/AAC.01608-21. Epub 2021 Nov 29.

Sasaki T(1), Svensson EM(2)(3), Wang X(4), Wang Y(4), Hafkin J(4), Karlsson MO(2), Mallikaarjun S(4).

A population pharmacokinetic analysis of delamanid and its major metabolite DM-6705 was conducted to characterize the pharmacokinetics of delamanid and DM-6705 in pediatric participants with multidrug-resistant tuberculosis (MDR-TB). Data from participants between the ages of 0.67 and 17 years, enrolled in 2 clinical trials, were utilized for the analysis. The final data set contained 634 delamanid and 706 DM-6705 valid plasma concentrations from 37 children. A transit model with three compartments best described the absorption of delamanid. Two-compartment models for each component with linear elimination were selected to characterize the dispositions of delamanid and DM-6705, respectively. The covariates included in the model were body weight on the apparent volume of distribution and apparent clearance (for both delamanid and DM-6705); formulation (dispersible versus film-coated tablet) on the mean absorption time; age, formulation, and dose on the bioavailability of delamanid; and age on the fraction of delamanid metabolized to DM-6705. Based on the simulations, doses for participants within different age/weight groups that result in delamanid exposure comparable to that in adults following the approved adult dose were calculated. By concentration-QTc (QTcB [QT corrected by Bazett's formula]) analysis, a significant positive correlation was detected with concentrations of DM-6705. However, the model-predicted upper bounds of the 90% confidence intervals of ΔQTc values were <10 ms at the simulated maximum concentration (Cmax) of DM-6705 following the administration of the maximum doses simulated. This suggests that the effect on the QT interval following the proposed dosing is unlikely to be clinically meaningful in children with MDR-TB who receive delamanid.

DOI: 10.1128/AAC.01608-21
PMID: 34843388

5. **Anti-tuberculosis drug resistance in Slovakia, 2018-2019: The first whole-genome epidemiological study.**

J Clin Tuberc Other Mycobact Dis. 2021 Dec 20;26:100292. doi: 10.1016/j.jctube.2021.100292. eCollection 2022 Feb.

Dohál M(1), Dvořáková V(2), Šperková M(2), Porvazník I(3)(4), Cabibbe AM(5), Trovato A(5), Spitaleri A(5), Rasmussen EM(6), Pršo K(1), Škereňová M(7), Cirillo DM(5), Solovič I(3), Mokrý J(1).

OBJECTIVE: The resistance of Mycobacterium (M.) tuberculosis to antituberculosis

drugs poses a major threat to global public health. Whole genome sequencing (WGS) is an increasingly preferred method in the diagnostics and monitoring of the transmission dynamics of resistant forms of tuberculosis (TB). The aim of the study was to, for the first time, use the sequencing-based analysis to study the transmission and resistance patterns of a systematic and recent collection of extensively drug resistant (XDR) and multidrug resistant tuberculosis (MDR-TB) isolates and to expand our knowledge about drug resistant (DR) TB epidemiological dynamics in Slovakia.
DESIGN: A total of 495 patients with pulmonary TB, who were referred to National Reference Laboratory for Mycobacteriology (Vyšné Hágy, Slovakia) in the years 2018-2019, were studied. Out of the total of 495 patients, 4 XDR-TB (0.8%) and 8 (1.6%) MDR-TB isolates were identified by conventional drug susceptibility testing on Löwenstein-Jensen solid medium and subjected to whole genome sequencing. Sequencing data were evaluated for molecular-epidemiological analysis and identification of resistance patterns.
RESULTS: Phylogenetic and cluster analysis showed extensive recent transmission events and the predominance of Euro-American lineage 4.7 in Slovakia. However, phylogenetic analysis revealed the circulation of several lineages that originally occurred in Eastern European countries. Resistance patterns for first- and second-line antituberculosis drugs characterized by whole genome sequencing were in high concordance with the results of phenotypic drug susceptibility testing.
CONCLUSION: Forty percent of at least MDR-TB isolates were not genetically linked, indicating that appropriate measures should be taken to monitor and prevent the spread of drug-resistant tuberculosis within the country as well as in other regions.

DOI: 10.1016/j.jctube.2021.100292
PMCID: PMC8717600
PMID: 35005254

6. **Comparative genomic analyses of multi-drug resistant Mycobacterium tuberculosis from Nepal and other geographical locations.**

Genomics. 2022 Feb 7;114(2):110278. doi: 10.1016/j.ygeno.2022.110278. Online ahead of print.

Leong KWC(1), Gautam SS(2), Pradhan M(3), Singh YI(3), Kc R(4), Rajbhandari SK(5), Ghimire GR(5), Adhikari K(5), Shrestha U(5), Chaudhary R(3), Ghimire G(3), Khadka S(6), O'Toole RF(7).

Nepal exhibits a tuberculosis (TB) incidence rate that is comparable to neighbouring high TB incidence countries. In addition, it records >500 cases of multi-drug resistant (MDR) TB each year. The objective of this study was to perform whole-genome bioinformatic analysis on MDR-TB isolates from Nepal (n = 19) to identify the specific mutations underlying their phenotypic resistance. In addition, we examined the dominant genotype among the Nepal MDR-TB isolates, the East-Asian Beijing sub-lineage, to determine its relatedness to a panel of 1274 genomes of international strains available from public databases. These analyses provided evidence that the XDR-TB isolates in our collection were not derived from importation of primary XDR-TB to Nepal but were more likely the result of acquisition of second-line drug resistance in Nepal. Resistance to fluoroquinolones was detected among a high proportion of the Nepal isolates. This has implications for the management of TB, including appropriate antimicrobial stewardship and susceptibility testing for fluoroquinolones and other second-line TB drugs, to minimise the development of XDR-TB among Nepal TB cases.

DOI: 10.1016/j.ygeno.2022.110278
PMID: 35143885

7. **Multi-drug-resistant tuberculosis clusters in Mpumalanga province, South Africa, 2013-2016: A spatial analysis.**

Trop Med Int Health. 2022 Feb;27(2):185-191. doi: 10.1111/tmi.13708. Epub 2022 Jan 13.

Mashamba MA(1), Tanser F(2)(3)(4)(5), Afagbedzi S(6), Beke A(1).

OBJECTIVE: To identify spatial clusters with unusually high levels of MDR-TB, which are highly unlikely to have arisen by chance in Mpumalanga Province, South Africa.
METHODS: Home addresses of all MDR-TB patients were collected from four MDR-TB facilities from 2013 to 2016. We mapped all addresses, linking them to the nearest ward with population estimates. A spatial analysis was conducted using kernel density in ArcGIS to estimate and map the distribution of the disease and used Gertis-Ord Gi to test for significant clustering.
RESULTS: A total of 4065 MDR-TB patients were mapped. Ten significant clusters (p-value <0.05) were found across the province in six sub-districts: Mbombela, Nkomazi, Emalahleni, Govan Mbeki, Lekwa and Mkhondo. Mbombela has the highest number of significant clusters. The central region did not have any MDR-TB clusters.

CONCLUSION: There is clear evidence of MDR-TB clustering in Mpumalanga. This calls for concentrated TB prevention efforts and proper allocation of resources. Further investigations are needed to identify MDR-TB predictors.

DOI: 10.1111/tmi.13708
PMID: 34873790

8. **A Scoping Review of the Clinical Pharmacokinetics of Bedaquiline.**

Clin Pharmacokinet. 2022 Jan 27. doi: 10.1007/s40262-022-01107-4. Online ahead of print.

Wilby KJ(1).

Tuberculosis continues to be a major infectious disease burden worldwide. Increasing drug resistance to first-line agents is making treatment more difficult. Bedaquiline is an orally administered drug active against Mycobacterium tuberculosis and is indicated for patients with confirmed multi-drug-resistant tuberculosis. This review aims to identify published literature reporting on the pharmacokinetics of bedaquiline, with a focus on key factors and drug interactions that may affect its use. Findings identified multiple areas for future study. First, exposure-response relationships should be further developed to determine the best ways to monitor both efficacy and safety. Second, dosing may be optimized through greater understanding of specific factors that may influence observed concentrations, including patient demographics and comorbidities. Finally, firm guidance for co-administration of bedaquiline with other drugs known to induce or inhibit cytochrome P450 enzymes is urgently required.

DOI: 10.1007/s40262-022-01107-4
PMID: 35083732

9. **Psychiatric comorbidities among patients with complex drug-resistant tuberculosis in Mumbai, India.**

PLoS One. 2022 Feb 11;17(2):e0263759. doi: 10.1371/journal.pone.0263759.

eCollection 2022.

Laxmeshwar C(1), Das M(1), Mathur T(1), Israni T(1), Jha S(1), Iyer A(1), Morales M(1), Decroo T(2), Gils T(2), Ferlazzo G(3), Iakovidi K(3), Garcia M(3), Isaakidis P(3).

BACKGROUND: People with drug-resistant tuberculosis (DR-TB) are known to suffer from many mental-health disorders. This study aims to describe the proportion of patients diagnosed with psychiatric comorbidities, the different psychiatric diagnoses made, and treatment outcomes among DR-TB patients with or without psychiatric comorbidity and initiated on DR-TB treatment between January 2012 and March 2019 at Médecins Sans Frontières independent clinic in Mumbai, India.
METHODS: This is a retrospective study using routinely collected clinical data. DR-TB care included individualised treatment, psychosocial support, and integrated psychiatric care.
RESULTS: During the study period, 341 DR-TB patients were enrolled, with a median age of 25 years (IQR:20.0-36.5 years), 185 (54.2%) females, 143 (41.9%) with PreXDR-TB, and 140 (41.0%) with XDR-TB. All 341 patients were screened by a counsellor, 119 (34.9%) were referred for psychiatric evaluation, and 102 (29.9% of 341) were diagnosed with a psychiatric comorbidity. Among 102 diagnosed with a psychiatric comorbidity, 48 (47.0%) were diagnosed at baseline, and 86 (84.3%), or 25.2% of all 341 patients enrolled, were treated with psychotropic drugs. Depressive disorders were diagnosed in 49 (48.0%), mixed anxiety and depression in 24 (23.5%), neurocognitive disorders and anxiety in five (4.9%), and medication induced psychosis in two (2.0%). No anti-TB drugs were significantly associated with psychiatric comorbidities developed during treatment. Of 102 DR-TB patients with a psychiatric comorbidity, 75.5% (77) had successful DR-TB treatment outcomes, compared to 61.1% (146/239) not diagnosed with a psychiatric comorbidity ($p = 0.014$).
CONCLUSION: In our setting, among people started on DR-TB treatment, and with a complex TB resistance profile, about one in three patients experienced a psychiatric comorbidity, of which half developed this comorbidity during treatment. With comprehensive psychiatric care integrated into DR-TB care delivery, treatment outcomes were at least as good among those with psychiatric comorbidities compared to those without such comorbidities.

DOI: 10.1371/journal.pone.0263759
PMCID: PMC8836323
PMID: 35148328

10. **Delamanid or pretomanid? A Solomonic judgement!**

J Antimicrob Chemother. 2022 Jan 28:dkab505. doi: 10.1093/jac/dkab505. Online

ahead of print.

Mudde SE(1), Upton AM(2), Lenaerts A(3), Bax HI(1)(4), De Steenwinkel JEM(1).

Given the low treatment success rates of drug-resistant tuberculosis (TB), novel TB drugs are urgently needed. The landscape of TB treatment has changed considerably over the last decade with the approval of three new compounds: bedaquiline, delamanid and pretomanid. Of these, delamanid and pretomanid belong to the same class of drugs, the nitroimidazoles. In order to close the knowledge gap on how delamanid and pretomanid compare with each other, we summarize the main findings from preclinical research on these two compounds. We discuss the compound identification, mechanism of action, drug resistance, in vitro activity, in vivo pharmacokinetic profiles, and preclinical in vivo activity and efficacy. Although delamanid and pretomanid share many similarities, several differences could be identified. One finding of particular interest is that certain Mycobacterium tuberculosis isolates have been described that are resistant to either delamanid or pretomanid, but with preserved susceptibility to the other compound. This might imply that delamanid and pretomanid could replace one another in certain regimens. Regarding bactericidal activity, based on in vitro and preclinical in vivo activity, delamanid has lower MICs and higher mycobacterial load reductions at lower drug concentrations and doses compared with pretomanid. However, when comparing in vivo preclinical bactericidal activity at dose levels equivalent to currently approved clinical doses based on drug exposure, this difference in activity between the two compounds fades. However, it is important to interpret these comparative results with caution knowing the variability inherent in preclinical in vitro and in vivo models.

DOI: 10.1093/jac/dkab505
PMID: 35089314

11. **Disseminated drug-resistant tuberculosis and multiple autoimmune syndrome in a child with selective IgA deficiency-An uncustomary combination.**

Int J Rheum Dis. 2022 Jan 20. doi: 10.1111/1756-185X.14289. Online ahead of print.

Nori H(1), Vohra V(1), Banday AZ(1), Jindal AK(1), Tyagi R(1), Sodhi MK(2), Bal A(3), Suri D(1).

Polyautoimmunity or multiple autoimmune syndrome (MAIS) is increasingly being recognized in pediatric clinical practice, often in conjunction with systemic lupus erythematosus (SLE). Besides multi-organ autoimmunity, children with SLE are often at a higher risk of developing infections including tuberculosis. The tendency to develop infections and multiple autoimmune diseases in childhood SLE often occurs in the absence of monogenic primary immunodeficiency disease. Conversely, children with inborn errors of immunity, of which selective IgA deficiency (sIgAD) is the most common, may develop recurrent infections and autoimmune disorders including SLE. Herein, we report a child with MAIS (including SLE) and sIgAD who developed drug-resistant tuberculosis, which was managed successfully with second-line anti-tubercular drug therapy. To the best of our knowledge, this combination of rare findings has not been reported previously in the pediatric literature. Although a majority of patients with sIgAD are either asymptomatic or have mild infections/autoimmunity, the index child had a myriad of infectious illnesses and multi-organ autoimmunity. Our case highlights the prudence of thoroughly evaluating children with SLE for other autoimmune diseases and vice versa. Given the higher probability of inherited disorders, including early complement deficiencies and monogenic interferonopathies, in childhood SLE compared with adult SLE, it may be prudent to perform a basic immunological workup (for example, immunoglobulin levels, 50% hemolytic complement) in such patients. A more extensive immunological and genetic evaluation (including next-generation sequencing) may also be required in the presence of unusual clinical or laboratory features, a positive family history, or a complicated clinical course.

DOI: 10.1111/1756-185X.14289
PMID: 35048520

12. **Tuberculosis drug discovery: Progression and future interventions in the wake of emerging resistance.**

Eur J Med Chem. 2022 Feb 5;229:114066. doi: 10.1016/j.ejmech.2021.114066. Epub 2021 Dec 26.

Perveen S(1), Kumari D(1), Singh K(1), Sharma R(2).

The emergence of drug resistance continues to afflict TB control where drug resistant strains have become a global health concern. Contrary to drug-sensitive TB, the treatment of MDR/XDR-TB is more complicated requiring the administration of second-line drugs that are inefficient than the first line

drugs and are associated with greater side effects. The emergence of drug resistant Mtb strains had coincided with an innovation void in the field of drug discovery of anti-mycobacterials. However, the approval of bedaquiline and delamanid recently for use in MDR/XDR-TB has given an impetus to the TB drug discovery. The review discusses the drug discovery efforts in the field of tuberculosis with a focus on the strategies adopted and challenges confronted by TB research community. Here, we discuss the diverse clinical candidates in the current TB drug discovery pipeline. There is an urgent need to combat the current TB menace through multidisciplinary approaches and strategies making use of the recent advances in understanding the molecular biology and pathogenesis of Mtb. The review highlights the recent advances in drug discovery, with the host directed therapeutics and nanoparticles-drug delivery coming up as important tools to fight tuberculosis in the future.

DOI: 10.1016/j.ejmech.2021.114066
PMID: 34973508 [Indexed for MEDLINE]

13. **Linezolid toxicity in patients with drug-resistant tuberculosis: a prospective cohort study.**

J Antimicrob Chemother. 2022 Feb 2:dkac019. doi: 10.1093/jac/dkac019. Online ahead of print.

Wasserman S(1)(2), Brust JCM(3), Abdelwahab MT(4), Little F(5), Denti P(4), Wiesner L(4), Gandhi NR(6)(7), Meintjes G(1)(8), Maartens G(1)(4).

BACKGROUND: Linezolid is recommended for treating drug-resistant TB. Adverse events are a concern to prescribers but have not been systematically studied at the standard dose, and the relationship between linezolid exposure and clinical toxicity is not completely elucidated.
PATIENTS AND METHODS: We conducted an observational cohort study to describe the incidence and determinants of linezolid toxicity, and to determine a drug exposure threshold for toxicity, among patients with rifampicin-resistant TB in South Africa. Linezolid exposures were estimated from a population pharmacokinetic model. Mixed-effects modelling was used to analyse toxicity outcomes.
RESULTS: One hundred and fifty-one participants, 63% HIV positive, were enrolled and followed for a median of 86 weeks. Linezolid was permanently discontinued for toxicity in 32 (21%) participants. Grade 3 or 4 linezolid-associated adverse events occurred in 21 (14%) participants. Mean haemoglobin concentrations increased with time on treatment (0.03 g/dL per week; 95% CI 0.02-0.03).

Linezolid trough concentration, male sex and age (but not HIV positivity) were independently associated with a decrease in haemoglobin >2 g/dL. Trough linezolid concentration of 2.5 mg/L or higher resulted in optimal model performance to describe changing haemoglobin and treatment-emergent anaemia (adjusted OR 2.9; 95% CI 1.3-6.8). SNPs 2706A>G and 3010G>A in mitochondrial DNA were not associated with linezolid toxicity.
CONCLUSIONS: Permanent discontinuation of linezolid was common, but linezolid-containing therapy was associated with average improvement in toxicity measures. HIV co-infection was not independently associated with linezolid toxicity. Linezolid trough concentration of 2.5 mg/L should be evaluated as a target for therapeutic drug monitoring.

DOI: 10.1093/jac/dkac019
PMID: 35134182

14. **First outbreak of multi-drug resistant tuberculosis (MDR-TB) in Denmark involving six Danish-born cases.**

Int J Infect Dis. 2022 Feb 11:S1201-9712(22)00095-9. doi: 10.1016/j.ijid.2022.02.017. Online ahead of print.

Suppli CH(1), Norman A(1), Folkvardsen DB(1), Gissel TN(2), Weinreich UM(3), Koch A(4), Wejse C(5), Lillebaek T(6).

BACKGROUND: Denmark is a tuberculosis (TB) and multi-drug resistant (MDR) TB low-incidence country at 5 and 0.05 cases per 100.000 population, respectively. Until 2018, transmission of MDR-TB was nonexistent except for few pairwise related family-cases. In this study we describe the first MDR-TB outbreak in Denmark.
METHODS: Based on genotyping of all Mycobacterium tuberculosis (Mtb) culture-positive cases in Denmark spanning three decades, six molecular- and epidemiologically linked Danish-born cases were identified as the first cluster of MDR-TB in Denmark. The primary case was diagnosed posthumously in 2010 followed by five epidemiologically linked cases from 2018 through 2019.
RESULTS AND CONCLUSION: Through a combination of routine Mtb genotyping and clinical epidemiological surveillance data, we identified the first Danish MDR-TB outbreak spanning 10 years and were able to disclose the specific transmission pathways in detail guiding the outbreak investigations. The occurrence of an MDR-TB outbreak in a resource rich TB low incidence setting

like Denmark, highlights the importance of a collaborative control system combining classical contact tracing; timely identification of drug resistant TB through rapid diagnostics; and a close collaboration between clinicians, classical- and molecular epidemiologists for the benefit of TB control.

DOI: 10.1016/j.ijid.2022.02.017
PMID: 35158061

15. **Model-Based Efficacy and Toxicity Comparisons of Moxifloxacin for Multidrug-Resistant Tuberculosis.**

Open Forum Infect Dis. 2021 Dec 29;9(3):ofab660. doi: 10.1093/ofid/ofab660. eCollection 2022 Mar.

Yun HY(1), Chang V(2), Radtke KK(2), Wang Q(2), Strydom N(2), Chang MJ(3)(4)(5), Savic RM(2).

BACKGROUND: Moxifloxacin (MOX) is used as a first-choice drug to treat multidrug-resistant tuberculosis (MDR-TB); however, evidence-based dosing optimization should be strengthened by integrative analysis. The primary goal of this study was to evaluate MOX efficacy and toxicity using integrative model-based approaches in MDR-TB patients.
METHODS: In total, 113 MDR-TB patients from 5 different clinical trials were analyzed for the development of a population pharmacokinetics (PK) model. A final population PK model was merged with a previously developed lung-lesion distribution and QT prolongation model. Monte Carlo simulation was used to calculate the probability target attainment value based on concentration. An area under the concentration-time curve (AUC)-based target was identified as the minimum inhibitory concentration (MIC) of MOX isolated from MDR-TB patients.
RESULTS: The presence of human immunodeficiency virus (HIV) increased clearance by 32.7% and decreased the AUC by 27.4%, compared with HIV-negative MDR-TB patients. A daily dose of 800 mg or a 400-mg, twice-daily dose of MOX is expected to be effective in MDR-TB patients with an MIC of ≤0.25 μg/mL, regardless of PK differences resulting from the presence of HIV. The effect of MOX in HIV-positive MDR-TB patients tended to be decreased dramatically from 0.5 μg/mL, in contrast to the findings in HIV-negative patients. A regimen of twice-daily doses of 400 mg should be considered safer than an 800-mg once-daily dosing regimen, because of the narrow fluctuation of concentrations.
CONCLUSIONS: Our results suggest that a 400-mg, twice-daily dose of MOX is an optimal dosing regimen for MDR-TB patients because it provides superior efficacy and safety.

DOI: 10.1093/ofid/ofab660
PMCID: PMC8825669
PMID: 35146045

16. **Drug-Resistant Characteristics, Genetic Diversity, and Transmission Dynamics of Rifampicin-Resistant Mycobacterium tuberculosis in Hunan, China, Revealed by Whole-Genome Sequencing.**

Microbiol Spectr. 2022 Feb 16;10(1):e0154321. doi: 10.1128/spectrum.01543-21. Online ahead of print.

He W(1), Tan Y(2), Liu C(3), Wang Y(1), He P(1), Song Z(1), Liu D(3)(4), Zheng H(5), Ma A(1), Zhao B(3), Ou X(3), Xia H(3), Wang S(3), Zhao Y(3).

To gain a deep insight into the additional drug-resistant profiles, genetic diversity, and transmission dynamics of rifampicin-resistant tuberculosis (RR-TB) circulating in Hunan province, drug susceptibility testing and whole-genome-sequencing were performed among RR-TB strains collected from Jan. 2013 to Jun. 2018 in Hunan province. A total of 124 RR-TB strains were recovered successfully and included into the final analysis. Lineage 2.2.1 was the dominant sublineage, accounting for 72.6% (90/124), followed by lineage 4.5 (11.3%, 14/124), lineage 4.4 (8.1%, 10/124), lineage 4.2 (6.5%, 8/124) and lineage 2.2.2 (1.6%, 2/124). Overall, 83.1% (103/124) and 3.2% (4/124) of RR-TB were MDR-TB and XDR-TB, respectively. Nearly 30% of RR-TB isolates were resistant to fluoroquinolones, and 26.6% (33/124) were pre-XDR-TB. Moreover, 30.6% (38/124) of RR-TB strains were identified as phenotypically resistance to pyrazinamide. Totally, 17 clusters containing 48 (38.7%, 48/124) RR-TB strains were identified, ranging in size from 2 to 10 isolates. No significant difference was detected in clustering rate between lineage 2 and lineage 4 ($\chi 2$ = 0.027, P = 0.870). Our study revealed the complexity of RR-TB strains circulating in Hunan province with complex additional drug-resistant profile and relatively higher clustering rates. Comprehensive information based on WGS should be used to guide the design of treatment regimens and tailor public interventions. IMPORTANCE Comprehensive information such as genetic background and drug-resistant profile of MTB strains could help to tailor public interventions. However, these data are limited in Hunan province, one of the provinces with high-TB burden in China. So, this study aimed to provide us with deep insight into the molecular epidemiology of RR-TB isolates circulating in Hunan province by combining phenotypic drug susceptibility testing and

whole-genome sequencing. To our knowledge, this is the first study to use whole-genome sequencing data of RR-TB strains spanning more than 5 years for molecular epidemiology analysis in Hunan province, which allows us to identify genetic background information and clustered strains more accurately. Our study revealed the complexity of RR-TB strains circulating in Hunan province with complex additional drug-resistant profile and relatively higher clustering rates. Comprehensive information based on WGS should be used to guide the design of treatment regimens and tailor public interventions.

DOI: 10.1128/spectrum.01543-21
PMCID: PMC8849054
PMID: 35171016

17. **Screening approaches and therapeutic targets: The two driving wheels of tuberculosis drug discovery.**

Biochem Pharmacol. 2022 Mar;197:114906. doi: 10.1016/j.bcp.2021.114906. Epub 2022 Jan 4.

Perveen S(1), Sharma R(2).

Tuberculosis (TB) is an infectious disease, infecting a quarter of world's population. Drug resistant TB further exacerbates the grim scenario of the drying TB drug discovery pipeline. The limited arsenal to fight TB presses the need for thorough efforts for identifying promising hits to combat the disease. The review highlights the efforts in the field of tuberculosis drug discovery, with an emphasis on massive drug screening campaigns for identifying novel hits against Mtb in both industry and academia. As an intracellular pathogen, mycobacteria reside in a complicated intracellular environment with multiple factors at play. Here, we outline various strategies employed in an effort to mimic the intracellular milieu for bringing the screening models closer to the actual settings. The review also focuses on the novel targets and pathways that could aid in target-based drug discovery in TB. The recent high throughput screening efforts resulting in the identification of potent hits against Mtb has been summarized in this article. There is a pressing need for effective screening strategies and approaches employing innovative tools and recent technologies; including nanotechnology, gene-editing tools such as CRISPR-cas system, host-directed bacterial killing and high content screening to augment the TB drug discovery pipeline with safer and shorter drug regimens.

DOI: 10.1016/j.bcp.2021.114906

PMID: 34990594

18. **Treatment outcomes of patients with MDR-TB and its determinants at referral hospitals in Ethiopia.**

PLoS One. 2022 Feb 17;17(2):e0262318. doi: 10.1371/journal.pone.0262318. eCollection 2022.

Wakjira MK(1), Sandy PT(2), Mavhandu-Mudzusi AH(3).

BACKGROUND: There is limited empirical evidence in Ethiopia on the determinants of treatment outcomes of patients with multidrug-resistant tuberculosis (MDR-TB) who were enrolled to second-line anti-tuberculosis drugs. Thus, this study investigated the determinants of treatment outcomes in patients with MDR-TB at referral hospitals in Ethiopia.
DESIGN AND METHODS: This study was underpinned by a cross-sectional quantitative research design that guided both data collection and analysis. Data is collected using structured questionnaire and data analyses was performed using the Statistical Package for Social Sciences. Multi-variable logistic regression was used to control for confounders in determining the association between treatment outcomes of patients with MDR-TB and selected predictor variables, such as co-morbidity with MDR-TB and body mass index.
RESULTS: From the total of 136 patients with MDR-TB included in this study, 31% had some co-morbidity with MDR-TB at baseline, and 64% of the patients had a body mass index of less than 18.5 kg/m2. At 24 months after commencing treatment, 76 (69%), n = 110), of the patients had successfully completed treatment, while 30 (27%) died of the disease. The odds of death was significantly higher among patients with low body mass index (AOR = 2.734, 95% CI: 1.01-7.395; P<0.048) and those with some co-morbidity at baseline (AOR = 4.260, 95%CI: 1.607-11.29; p<0.004).
CONCLUSION: The higher proportion of mortality among patients treated for MDR-TB at Adama and Nekemte Hospitals, central Ethiopia, is attributable to co-morbidities with MDR-TB, including HIV/AIDS and malnutrition. Improving socio-economic and nutritional support and provision of integrated care for MDR-TB and HIV/AIDS is recommended to mitigate the higher level of death among patients treated for MDR-TB.

DOI: 10.1371/journal.pone.0262318
PMCID: PMC8853509
PMID: 35176035

19. **Multidrug-resistant tuberculosis control in Rwanda overcomes a successful clone**

that causes most disease over a quarter century.

J Clin Tuberc Other Mycobact Dis. 2022 Jan 24;27:100299. doi: 10.1016/j.jctube.2022.100299. eCollection 2022 May.

Ngabonziza JCS(1)(2)(3), Rigouts L(2)(4), Torrea G(2), Decroo T(5)(6), Kamanzi E(1), Lempens P(2)(4), Rucogoza A(1), Habimana YM(7), Laenen L(8), Niyigena BE(1), Uwizeye C(2), Ushizimpumu B(1), Mulders W(2), Ivan E(1), Tzfadia O(2), Muvunyi CM(3), Migambi P(6), Andre E(2)(8)(9), Mazarati JB(10), Affolabi D(11), Umubyeyi AN(12), Nsanzimana S(13), Portaels F(2), Gasana M(7), de Jong BC(2), Meehan CJ(2)(14).

SUMMARY BACKGROUND: Multidrug-resistant (MDR) tuberculosis (TB) poses an important challenge in TB management and control. Rifampicin resistance (RR) is a solid surrogate marker of MDR-TB. We investigated the RR-TB clustering rates, bacterial population dynamics to infer transmission dynamics, and the impact of changes to patient management on these dynamics over 27 years in Rwanda.
METHODS: We analysed whole genome sequences of a longitudinal collection of nationwide RR-TB isolates. The collection covered three important periods: before programmatic management of MDR-TB (PMDT; 1991-2005), the early PMDT phase (2006-2013), in which rifampicin drug-susceptibility testing (DST) was offered to retreatment patients only, and the consolidated phase (2014-2018), in which all bacteriologically confirmed TB patients had rifampicin DST done mostly via Xpert MTB/RIF assay. We constructed clusters based on a 5 SNP cut-off and resistance conferring SNPs. We used Bayesian modelling for dating and population size estimations, TransPhylo to estimate the number of secondary cases infected by each patient, and multivariable logistic regression to assess predictors of being infected by the dominant clone.
RESULTS: Of 308 baseline RR-TB isolates considered for transmission analysis, the clustering analysis grouped 259 (84.1%) isolates into 13 clusters. Within these clusters, a single dominant clone was discovered containing 213 isolates (82.2% of clustered and 69.1% of all RR-TB), which we named the "Rwanda Rifampicin-Resistant clone" (R3clone). R3clone isolates belonged to Ugandan sub-lineage 4.6.1.2 and its rifampicin and isoniazid resistance were conferred by the Ser450Leu mutation in rpoB and Ser315Thr in katG genes, respectively. All R3clone isolates had Pro481Thr, a putative compensatory mutation in the rpoC gene that likely restored its fitness. The R3clone was estimated to first arise in 1987 and its population size increased exponentially through the 1990s', reaching maximum size (∼84%) in early 2000 s', with a declining trend since 2014. Indeed, the highest proportion of R3clone (129/157; 82·2%, 95%CI: 75·3-87·8%) occurred between 2000 and 13, declining to 64·4% (95%CI: 55·1-73·0%) from 2014 onward. We showed that patients with R3clone detected after an unsuccessful category 2 treatment were more likely to generate secondary cases than patients with R3clone detected after an unsuccessful category 1 treatment

regimen.
CONCLUSIONS: RR-TB in Rwanda is largely transmitted. Xpert MTB/RIF assay as first diagnostic test avoids unnecessary rounds of rifampicin-based TB treatment, thus preventing ongoing transmission of the dominant R3clone. As PMDT was intensified and all TB patients accessed rifampicin-resistance testing, the nationwide R3clone burden declined. To our knowledge, our findings provide the first evidence supporting the impact of universal DST on the transmission of RR-TB.

DOI: 10.1016/j.jctube.2022.100299
PMCID: PMC8802117
PMID: 35146133

20. **Transmission of multidrug-resistant Mycobacterium tuberculosis in Wuhan, China: A retrospective molecular epidemiological study.**

Medicine (Baltimore). 2022 Jan 28;101(4):e28751. doi: 10.1097/MD.0000000000028751.

Duan Q(1), Zhang Z(1), Tian D(1), Zhou M(1), Hu Y(2), Wu J(3), Wang T(1), Li Y(4), Chen J(2).

How multidrug-resistant tuberculosis (MDR-TB) spreads and expands in Wuhan population is not clear. The study aimed to determine the transmission patterns of MDR-TB in Wuhan city, China, including 149 patients with MDR-TB.Tuberculosis isolates were genotyped by deletion-targeted multiplex polymerase chain reaction, mycobacterial interspersed repetitive unit-variable number tandem repeat typing, and sequencing of drug resistance-associated genes. The risk factors of genomic-clustering were analyzed with logistic regression. The genomic-clustering patients were deeply investigated.The analysis identified 111 unique and 11 clustered genotypes (38 isolates). The clustering rate was 25.50% and the minimum estimate proportion of recent transmission was 18.12%. Two clusters (5 isolates) shared the same mutation, the remain 9 clusters (33 isolates) had different mutation. Logistic regression showed that older than 60 years (adjusted OR 2.360, 95% CI:1.052-5.292) was an independent factor associated with the genomic-clustering of MDR-TB. Among the 38 genomic-clustering cases, 14 cases had epidemiological transmission links. The most common type of transmission link was social contact.The local transmission of MDR-TB in Wuhan was really an issue. The elderly population might be the high-risk groups for transmission of MDR-TB, and the community or public transportation might be the main transmission places.

DOI: 10.1097/MD.0000000000028751
PMCID: PMC8797475
PMID: 35089253 [Indexed for MEDLINE]

21. **Structural and Dynamic Insights into the W68L, L85P, and T87A Mutations of Mycobacterium tuberculosis Inducing Resistance to Pyrazinamide.**

Int J Environ Res Public Health. 2022 Jan 30;19(3):1615. doi: 10.3390/ijerph19031615.

Alatawi EA(1), Alshabrmi FM(2).

Tuberculosis (TB), the most frequent bacterium-mediated infectious disease caused by Mycobacterium tuberculosis, has been known to infect humans since ancient times. Although TB is common worldwide, the most recent report by the WHO (World Health Organization) listed the three countries of India, China, and Russia with 27%, 14%, and 8% of the global burden of TB, respectively. It has been reported that resistance to TB drugs, particularly by the pncA gene to the pyrazinamide drug due to mutations, significantly affects the effective treatment of TB. Understanding the mechanism of drug resistance using computational methods is of great interest to design effective TB treatment, exploring the structural features with these tools. Thus, keeping in view the importance of these methods, we employed state-of-the-art computational methods to study the mechanism of resistance caused by the W68L, L85P, and T87A mutations recently reported in 2021. We employed a molecular docking approach to predict the binding conformation and studied the dynamic properties of each complex using molecular dynamics simulation approaches. Our analysis revealed that compared to the wildtype, these three mutations altered the binding pattern and reduced the binding affinity. Moreover, the structural dynamic features also showed that these mutations significantly reduced the structural stability and packing, particularly by the W68L and L85P mutations. Moreover, principal component analysis, free energy landscape, and the binding free energy results revealed variation in the protein's motion and the binding energy. The total binding free energy was for the wildtype -9.61 kcal/mol, W68L -7.57 kcal/mol, L85P -6.99 kcal/mol, and T87A -7.77 kcal/mol. Our findings can help to design a structure-based drug against the MDR (multiple drug-resistant) TB.

DOI: 10.3390/ijerph19031615
PMCID: PMC8835092
PMID: 35162636

22. **Mycobacterium tuberculosis peritonitis in peritoneal dialysis patients: A scoping review.**

Nephrology (Carlton). 2022 Feb;27(2):133-144. doi: 10.1111/nep.13997. Epub 2021 Dec 6.

Thomson BKA(1)(2), Vaughan S(3), Momciu B(1).

BACKGROUND: The clinical syndrome of Mycobacterium tuberculosis (M. tuberculosis) peritoneal dialysis (PD) peritonitis is poorly understood. Whether local tuberculosis (TB) patterns modify the clinical syndrome, and what factors associate with poor outcomes is also unknown.
METHODS: A scoping review identified published cases of TB PD peritonitis. Cases from low- and high-TB burden areas were compared, and cases that did or did not suffer a poor clinical outcome were compared.
RESULTS: There were 216 cases identified. Demographics, presentation, diagnosis, treatment and outcomes were described. Significant delays in diagnosis were common (6.1 weeks) and were longer in patients from low-TB burden regions (7.3 vs. 3.7 weeks). In low-TB burden areas, slower diagnostic methods were more commonly used like PD fluid culture (64.3% vs. 32.7%), and treatment was less likely with quinolone antibiotics (6.9% vs. 34.1%). Higher national TB incidence and lower GDP per capita were found in cases that suffered PD catheter removal or death. Diagnostic delays were not longer in cases in which a patient suffered PD catheter removal or death. Cases that suffered death were older (51.9 vs. 45.1 years) and less likely female (37.8% vs. 55.7%). Removal of PD catheter was more common in cases in which a patient died (62.0% vs. 49.1%).
CONCLUSIONS: Outcomes in TB PD peritonitis are best predicted by national TB incidence, patient age and sex. Several unique features are identified to alert clinicians to use more rapid diagnostic methods that might enhance outcomes in TB PD peritonitis.

DOI: 10.1111/nep.13997
PMID: 34743395

23. **Application of Amplicon-Based Targeted NGS Technology for Diagnosis of Drug-Resistant Tuberculosis Using FFPE Specimens.**

Microbiol Spectr. 2022 Feb 9;10(1):e0135821. doi: 10.1128/spectrum.01358-21. Online ahead of print.

Song J(#)(1), Du W(#)(1), Liu Z(#)(1), Che J(1), Li K(1), Che N(1).

Next-generation sequencing (NGS) enables rapid identification of common and rare drug-resistant genetic variations from tuberculosis (TB) patients' sputum samples and MTB isolates. However, whether this technology is effective for formalin-fixed and paraffin-embedded (FFPE) tissues remains unclear. An amplicon-based targeted NGS sequencing panel was developed to predict susceptibility to 9 antituberculosis drugs, including 3 first-line drugs, by directly detecting FFPE tissues. A total of 178 tissue samples from TB patients who underwent phenotypic drug susceptibility test were retrospectively tested from January 2017 to October 2019 in the Department of Pathology, Beijing Chest Hospital, China. Phenotypic drug susceptibility test results were used as the reference standard. We identified 22 high-quality mutations from 178 FFPE tissue samples, including 15 high+moderate+minimal confidence-level mutations associated with drug resistance (rpoB D435V, S450F/L; KatG S315T; inhA-fabG promoter c-15t; embB G406S, M306V; rpsL K43R, K88R, rrs a1401g, a514c; gyrA D94G/Y/A, A90V), 6 mutations not associated with resistance (rpoB D435Y, H445S, L430P, L452P; embB G406A/D), and one mutation site embB M306I defined as indeterminate. Compared to the phenotypic method, sensitivities (95% CI) for rifampicin, isoniazid, and ethambutol were 96% (79.65-99.90%), 93.55% (78.58-99.21%), and 71.43% (35.24-92.44%), respectively; while for second-line drugs, it varied from 23.53% (9.05-47.77%) for capreomycin to 86.84% (72.20-94.72%) for streptomycin. Specificities for all drugs were satisfactory (>94.51%). Therefore, important pathological FFPE tissue samples, despite partially degraded DNA, can be used as essential specimens for molecular diagnosis of drug resistant TB by amplicon-based targeted NGS technology. IMPORTANCE Amplicon-based targeted NGS technology focuses on a set of gene mutations of known or suspected associations with drug susceptibility in Mycobacterium tuberculosis (MTB). This method offers many benefits, such as low sequencing cost, easy customization, high throughput, shorter testing time and not culture dependent. Formalin-fixed and paraffin-embedded (FFPE) tissues are important pathological specimen in diagnosing tuberculous disease because they are noninfectious and provide excellent preservation of tissue morphology with low storage cost. However, the performance of amplicon-based targeted NGS method on FFPE samples has not been reported yet. Therefore, we evaluated the performance of this method using FFPE samples collected from January 2017 to October 2019 in the Department of Pathology, Beijing Chest Hospital, China. We demonstrate that the amplicon-based targeted NGS method performs excellent on FFPE samples, and it can be applied to pathological diagnosis of drug resistant tuberculosis.

DOI: 10.1128/spectrum.01358-21
PMCID: PMC8826733

PMID: 35138166

24. **Anti-mycobacterial natural products and mechanisms of action.**

Nat Prod Rep. 2022 Jan 26;39(1):77-89. doi: 10.1039/d1np00011j.

Han J(1), Liu X(2), Zhang L(2), Quinn RJ(1), Feng Y(1).

Covering: up to June, 2020Tuberculosis (TB) continues to be a major disease with high mortality and morbidity globally. Drug resistance and long duration of treatment make antituberculosis drug discovery more challenging. In this review, we summarize recent advances on anti-TB natural products (NPs) and their potential molecular targets in cell wall synthesis, protein production, energy generation, nucleic acid synthesis and other emerging areas. We highlight compounds with activity against drug-resistant TB, and reveal several novel targets including Mtb biotin synthase, ATP synthase, 1,4-dihydroxy-2-naphthoate prenyltransferase and biofilms. These anti-TB NPs and their targets could facilitate target-based screening and accelerate TB drug discovery.

DOI: 10.1039/d1np00011j
PMID: 34226909

25. **Determinants of treatment outcomes in patients with multidrug-resistant TB.**

Int J Tuberc Lung Dis. 2022 Feb 1;26(2):126-132. doi: 10.5588/ijtld.21.0351.

Burhan E(1), Soepandi PZ(1), Isbaniah F(1), Damayanti K(1), Edwar SQ(1), Maruli MF(1), Ralena NA(2), Susanto AD(1).

BACKGROUND: Treating multidrug-resistant TB (MDR-TB) remains challenging. However, the determinants and timing of poor outcomes during MDR-TB treatment are still poorly understood.METHODS: We conducted a retrospective cohort study on all adult MDR-TB patients treated at Persahabatan Hospital, Jakarta, Indonesia, between January 2013 and December 2016. Risk factors for poor outcomes were analysed using Cox regression.RESULTS: Death occurred at a median time of 6 months (IQR 4-14) and loss to follow-up (LTFU) at 7 months (IQR 3-11). In multivariate analysis, advanced age (aHR 2.91, 95% CI 1.21-6.96; P = 0.017 for age >60 years), having diabetes mellitus (aHR 2.18, 95% CI 1.25-3.82; P = 0.006) and HIV co-infection (aHR 3.73, 95% CI 1.14-12.23; P = 0.030) were predictive of poor outcome in the first 7 months of treatment, whereas history of LTFU (patients who were LTFU once: aHR 2.14, 95% CI 1.33-3.47; P = 0.002; patients who were LTFU more than once: aHR 3.61, 95% CI 1.68-7.77; P = 0.001)

and baseline body mass index <18.5 kg/m² (aHR 1.98, 95% CI 1.10-3.56; P = 0.022) predicted poor outcome after 7 months of treatment.CONCLUSION: Different subsets of patients with MDR-TB are at risk of poor outcome at different times during treatment.

DOI: 10.5588/ijtld.21.0351
PMID: 35086624

26. **COVID-19 Pandemic Disruption on the Management of Tuberculosis Treatment in Indonesia.**

J Multidiscip Healthc. 2022 Jan 26;15:175-183. doi: 10.2147/JMDH.S341130. eCollection 2022.

Caren GJ(1), Iskandar D(2)(3), Pitaloka DAE(1), Abdulah R(1)(4), Suwantika AA(1)(4)(5).

The current coronavirus disease 2019 (COVID-19) situation might deteriorate the efforts to eliminate tuberculosis (TB) in Indonesia. This study aimed to review the COVID-19 pandemic disruption on the management of TB treatment in Indonesia. We identified several disruptions due to the pandemic on TB control management. Firstly, there is a potential decrease in the funding for TB treatment. Financial disruptions caused by the COVID-19 pandemic have led to further setbacks. In many countries, including Indonesia, financial and other resources have been reallocated from TB to the COVID-19 response. Secondly, it has been highlighted that all TB services, including case detection and rapid diagnostic, have been disrupted by the pandemic. Thirdly, the pandemic would be associated with the lower quality of care and treatment for TB in Indonesia. It might decrease the enthusiasm of patients with TB, multi-drug resistant (MDR)-TB, and TB-human immunodeficiency virus (HIV) to visit TB hospitals because of social distancing measures by the government. Finally, the COVID-19 pandemic also has impacted critical activities of monitoring, evaluation, and surveillance. There are several lessons from other countries about managing TB treatment during the pandemic, such as combining screening for COVID-19 and TB by applying x-ray technology and artificial intelligence-based software. In addition, the use of telemedicine or telehealth in TB treatment is also beneficial to deliver medication, assess patients' progress, and inform prevention strategies. To reach the target with the end TB strategy, the government of Indonesia can adopt the World Health Organization's (WHO's) comprehensive strategies, such as integrated, patient-centered TB care and prevention strategies; bold policies and supportive systems; and intensified research and innovations.

DOI: 10.2147/JMDH.S341130
PMCID: PMC8801372
PMID: 35115781

27. **Pediatric tuberculosis in India: Justice and human rights.**

Public Health Nurs. 2022 Feb 13. doi: 10.1111/phn.13061. Online ahead of print.

Mannebach K(1), Dressel A(2), Eason L(2).

Tuberculosis (TB) is the deadliest infectious disease across the world, with the greatest burden occurring in India. Pregnant women and children are especially vulnerable to adverse effects from infection, and they tend to have diminished ability to protect themselves. Malnutrition, HIV, and other causes of immune suppression such as exposure to air pollution make one more prone to serious illness or death from TB infection. Risk factors are influenced by maternal education, access to health care, poverty, nutrition, healthcare stigma, and sanitation, among others. Current literature is heavily clinical, lacking focus on upstream factors, with a skew toward secondary and tertiary prevention strategies (i.e., case finding and treatment), and less emphasis on primary prevention (e.g., wealth equity and environmental regulation). Given concerns with extremely drug resistant TB and because infectious diseases can permeate National borders, public health nurses, and other healthcare professionals must educate themselves and advocate on behalf of vulnerable populations such as children in India. Improved sanitation, air quality monitoring, women's education, and increased access to health care are cost-effective and evidence-based strategies to address pediatric TB in India, a challenge which is grounded in human rights and justice.

DOI: 10.1111/phn.13061
PMID: 35152480

28. **A modeling-based proposal for safe and efficacious reintroduction of bedaquiline after dose interruption: A population pharmacokinetics study.**

CPT Pharmacometrics Syst Pharmacol. 2022 Jan 31. doi: 10.1002/psp4.12768. Online ahead of print.

Keutzer L(1), Akhondipour Salehabad Y(1), Davies Forsman L(2)(3), Simonsson

USH(1).

Bedaquiline (BDQ) is recommended for treatment of multidrug-resistant tuberculosis (MDR-TB) for the majority of patients. Given its long terminal half-life and safety concerns, such as QTc-prolongation, re-introducing BDQ after multiple dose interruption is not intuitive and there are currently no existing guidelines. In this simulation-based study, we investigated different loading dose strategies for BDQ re-introduction, taking safety and efficacy into account. Multiple scenarios of time and length of interruption as well as BDQ re-introduction, including no loading dose, 1- and 2-week loading doses (200 mg and 400 mg once daily), were simulated from a previously published population pharmacokinetic (PK) model describing BDQ and its main metabolite M2 PK in patients with MDR-TB. The efficacy target was defined as 95.0% of the average BDQ concentration without dose interruption during standard treatment. Because M2 is the main driver for QTc-prolongation, the safety limit was set to be below the maximal average M2 metabolite concentration in a standard treatment. Simulations suggest that dose interruptions between treatment weeks 3 and 72 (interruption length: 1 to 6 weeks) require a 2-week loading dose of 200 mg once daily in the typical patient. If treatment was interrupted for longer than 8 weeks, a 2-week loading dose (400 mg once daily) was needed to reach the proposed efficacy target, slightly exceeding the safety limit. In conclusion, we here propose a strategy for BDQ re-introduction providing guidance to clinicians for safe and efficacious BDQ dosing.

DOI: 10.1002/psp4.12768
PMID: 35102712

29. **High-dose gatifloxacin-based shorter treatment regimens for MDR/RR-TB.**

Int J Infect Dis. 2022 Feb;115:142-148. doi: 10.1016/j.ijid.2021.11.037. Epub 2021 Nov 30.

Nie Q(1), Tao L(2), Li Y(3), Chen N(4), Chen H(4), Zhou Y(4), Wang Y(4), Chen H(5), Tang Q(4), Wang X(6), Huang C(7), Yang C(8).

SETTING: The shorter treatment regimen (STR) for multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB) has achieved successful outcomes in many countries. However, there are few studies on high-dose gatifloxacin-based STR with adverse drug reactions (ADRs) and management.

DESIGN: A prospective observational study was conducted with MDR/RR-TB patients who were treated with a standardized 9 or 12 - month regimen: including gatifloxacin (Gfx), clofazimine (Cfz), ethambutol (EMB), and pyrazinamide (PZA), and supplemented by amikacin (Am), isoniazid (INH), and prothionamide (Pto) during an intensive phase of 4 or 6 - month. Monitored ADRs monthly until treatment completion and then followed up every three months for one year.
RESULTS: Among the 42 eligible patients, 35 (83.3%) completed treatment successfully, 1 (2.4%) lost to follow-up (LTFU), and 6 (14.3%) failed due to ADRs, with no death. The most important ADR was drug-induced liver damage, which occurred in 24 out of 42 (57.1%) patients and resulted in 4 (9.5%) failed treatments and 4 (9.5%) adjusted treatments. QT interval prolongation occurred in 17 out of 42 (40.5%) patients, 9 (21.4%) of them with the corrected QT interval according to Fridericia (QTcF) > 500 ms resulting in 7 (16.7%) adjusted treatments.
CONCLUSIONS: This study confirmed the effectiveness of the high-dose gatifloxacin-based STR but severe ADRs, especially hepatotoxicity and QT interval prolongation should never be ignored.

DOI: 10.1016/j.ijid.2021.11.037
PMID: 34861398 [Indexed for MEDLINE]

30. **Person-centred care and short oral treatment for rifampicin-resistant tuberculosis improve retention in care in Kandahar, Afghanistan.**

Trop Med Int Health. 2022 Feb;27(2):207-215. doi: 10.1111/tmi.13716. Epub 2022 Jan 17.

Mesic A(1)(2), Ishaq S(3), Khan WH(3), Mureed A(4), Mar HT(4), Khaing EE(4), Bermudez-Aza E(1), Rose L(3), Lynen L(2), Seddiq MK(5), Amirzada HK(5), Keus K(1), Decroo T(2)(6).

OBJECTIVES: To describe the effect of adaptations to a person-centred care with short oral regimens on retention in care for rifampicin-resistant TB (RR-TB) in Kandahar province, Afghanistan.
METHODS: The study included people with RR-TB registered in the programme between 01 October 2016 and 18 April 2021. From 19 November 2019, the programme implemented a trial investigating the safety and effectiveness of short oral RR-TB regimens. During the trial, person-centred care was adapted. We included the data from people living with RR-TB treated in the period before and after the care model was adapted and applied Kaplan-Meier statistics to compare rates of retention in care.

RESULTS: Of 236 patients registered in the RR-TB programme, 146 (61.9%) were registered before and 90 (38.1%) after the model of care was adapted. Before adaptations enhancing person-centred care, pre-treatment attrition was 23.3% (n = 34/146), whilst under the adapted care model it was 5.6% (n = 5/90). Attrition on treatment was 22.3% (n = 25/112) before adaptations, whilst during the study period none of the participants were lost-to-follow-up on treatment and 3.3% died (n = 3/90).
CONCLUSIONS: As person-centred care delivery and treatment regimens were adapted to better fit-specific contextual challenges and the needs of the target population, retention in care improved amongst people with RR-TB in Kandahar, Afghanistan.

DOI: 10.1111/tmi.13716
PMID: 34978748

31. **Assessment of Factors Associated with Unfavorable Outcomes among Drug-Resistant TB Patients: A 6-Year Retrospective Study from Pakistan.**

Int J Environ Res Public Health. 2022 Jan 29;19(3):1574. doi: 10.3390/ijerph19031574.

Khan FU(1)(2)(3)(4)(5), Rehman AU(5), Khan FU(1)(2)(3)(4), Hayat K(1)(2)(3)(4)(6), Khan A(5), Ahmad N(7), Chang J(1)(2)(3)(4), Malik UR(1)(2)(3)(4), Fang Y(1)(2)(3)(4).

The spread of drug-resistant tuberculosis (DR TB) poses significant challenges to the control and successful eradication of TB globally. The current retrospective study was designed to evaluate the treatment outcomes and identify the risk factors associated with unsuccessful outcomes among DR TB patients. A total of 277/308 eligible DR TB patients were enrolled for treatment at the programmatic management unit of DR TB at the Pakistan Institute of Medical Sciences, Islamabad between January 2014 and July 2019. Treatment outcomes were defined according to the WHO recommendations. Death, treatment failure, and lost to follow-up (LTFU) were collectively grouped as unsuccessful treatment outcomes, whereas cured and treatment completed were summed up together as successful treatment outcomes. Out of the total 277 patients, 265 (95.67%) were multidrug/rifampicin-resistant TB (MDR/RR-TB) cases, 8 (2.89%) were isoniazid resistant cases, and 4 (1.44%) were extensively drug-resistant ones. In the current cohort, a total of 177 (63.9%) achieved successful treatment outcomes. Among them, 153 (55.2%) were declared cured and 24 (8.7%) completed their

treatment. Of the remaining 100 (36.1%) patients with unsuccessful outcomes, 60 (21.7%) died, 32 (11.5%) were LTFU, and 8 (2.9%) had failed treatment. The proportion of male patients was relatively higher (55.2%), within the age group of 21-40 years (47.3%) and lived in rural areas (66.8%). The multivariate analysis revealed that unsuccessful outcomes had a statistically significant association with being male (adjusted odds ratio, AOR: 1.92, 95% confidence interval (CI): 1.10-3.36), being in an age group above 60 years (AOR: 3.34, 95% CI: 1.09-10.1), suffering from any comorbidity (AOR: 2.69, 95% CI: 1.35-5.38), and the history of use of second-line drugs (AOR; 3.51, 95% CI 1.35-9.12). In conclusion, treatment outcomes among DR TB patients at the study site were poor and did not achieve the treatment success target (≥75%) set by the World Health Organization.

DOI: 10.3390/ijerph19031574
PMCID: PMC8835434
PMID: 35162598

32. **Predictors of treatment outcomes among patients with multidrug-resistant tuberculosis in Vietnam: a retrospective cohort study.**

BMC Infect Dis. 2022 Jan 20;22(1):68. doi: 10.1186/s12879-021-06992-x.

Wrohan I(1)(2), Nguyen TA(3)(4), Nguyen VN(5), Nguyen BH(5), Hoang TTT(5), Nguyen PC(4), Velen K(3)(6), Marks GB(6)(7), Fox GJ(3)(6).

BACKGROUND: Improving treatment outcomes for multidrug-resistant tuberculosis (MDR-TB) is a leading priority for global TB control. This retrospective cohort study evaluated the factors associated with treatment success among patients treated for MDR-TB in two provinces in Vietnam.
METHODS: Treatment outcomes were evaluated for adult patients treated in Hanoi and Thanh Hoa provinces between 2014 and 2016. The primary outcome was the proportion of patients with treatment success, defined as cure or treatment completion. Logistic regression analysis was used to evaluate the relationship between patient clinical and microbiological characteristics and treatment success.
RESULTS: Treatment outcomes were reported in 612 of 662 patients; of these, 401 (65.5)% were successfully treated. The odds of treatment success were lower for male patients (aOR 0.56, 95% CI 0.34-0.90), for people living with HIV (aOR 0.44, 95% CI 0.20-1.00), and for patients treated for extensive antibiotic resistance (pre-XDR-/XDT-TB) (aOR 0.53, 95% CI 0.29-0.97), compared with others. Patients who achieved culture conversion in the first 4 months of treatment had increased odds (aOR 2.93, 95% CI 1.33-6.45) of treatment success. In addition, loss to follow-up was less common among patients covered by social health

insurance compared to those who paid for treatment out-of-pocket (aOR 0.55, 95% CI 0.32-0.95).
CONCLUSIONS: Among patients with MDR-TB, males, people living with HIV, and those with more extensive antibiotic resistance at diagnosis are at greatest risk of an unsuccessful treatment outcome. Efforts to optimise the management of co-morbidities (such as HIV), ensure rapid bacteriological conversion, and provide financial support for patients promise to improve treatment outcomes.

DOI: 10.1186/s12879-021-06992-x
PMCID: PMC8772201
PMID: 35057754 [Indexed for MEDLINE]

33. **Sudapyridine (WX-081), a Novel Compound against Mycobacterium tuberculosis.**

Microbiol Spectr. 2022 Feb 16;10(1):e0247721. doi: 10.1128/spectrum.02477-21. Online ahead of print.

Yao R(#)(1)(2), Wang B(#)(1)(2), Fu L(1)(2), Li L(3), You K(3), Li YG(3), Lu Y(1)(2).

Bedaquiline (BDQ) was historically listed by the World Health Organization (WHO) in 2018 as the preferred option for rifampin-resistant tuberculosis (RR-TB) and multidrug-resistant tuberculosis (MDR-TB). However, when there is no other effective regimen, the side effects and weaknesses of BDQ limit its use of MDR-TB. There is a black box warning in the package insert of BDQ to warn patients and health care professionals that this drug may increase the risk of unexplained mortality and QT prolongation, which may lead to abnormal and potentially fatal cardiac rhythm. In addition, the phenomenon of elevated liver enzymes in clinical trials of BDQ is a potential sign of hepatotoxicity. Therefore, it is still a medical need to develop new compounds with better safety profiles, patient compliance, affordability, and the ability to retain the efficacy of BDQ. After extensive lead generation and optimization, a new analog, sudapyridine (WX-081), was selected as a potential new antituberculosis candidate to move into clinical trials. Here, we evaluated WX-081's overall preclinical profile, including efficacy, pharmacokinetics, and toxicology. The in vitro activity of WX-081 against drug-sensitive and drug-resistant tuberculosis was comparable to that of BDQ, and there was comparable efficacy between WX-081 and BDQ in both acute and chronic mouse tuberculosis models using low-dose aerosol infection. Moreover, WX-081 improved pharmacokinetic parameters and, more importantly, had no adverse effects on blood pressure, heart rate, or qualitative ECG parameters from nonclinical toxicology studies. WX-081 is under

investigation in a phase 2 study in patients. IMPORTANCE This study is aimed at chemotherapy for multidrug-resistant tuberculosis (MDR-TB), mainly to develop new anti-TB drugs to kill Mycobacterium tuberculosis, a microorganism with strong drug resistance. In this study, the structure of a potent antituberculosis compound, bedaquiline (BDQ), was optimized to generate a new compound, sudapyridine (WX-081). This experiment showed that its efficacy was similar to that of BDQ, its cardiotoxicity was lower, and it had good kinetic characteristics. This compound will certainly achieve significant results in the control and treatment of tuberculosis in the future.

DOI: 10.1128/spectrum.02477-21
PMCID: PMC8849072
PMID: 35170994

34. **Tuberculosis drug resistance profiling based on machine learning: A literature review.**

Braz J Infect Dis. 2022 Feb 14:102332. doi: 10.1016/j.bjid.2022.102332. Online ahead of print.

Sharma A(1), Machado E(2), Lima KVB(3), Suffys PN(2), Conceição EC(4).

Tuberculosis (TB), caused by Mycobacterium tuberculosis (MTB), is one of the top 10 causes of death worldwide. Drug-resistant tuberculosis (DR-TB) poses a major threat to the World Health Organization's "End TB" strategy which has defined its target as the year 2035. In 2019, there were close to 0.5 million cases of DRTB, of which 78% were resistant to multiple TB drugs. The traditional culture-based drug susceptibility test (DST - the current gold standard) often takes multiple weeks and the necessary laboratory facilities are not readily available in low-income countries. Whole genome sequencing (WGS) technology is rapidly becoming an important tool in clinical and research applications including transmission detection or prediction of DR-TB. For the latter, many tools have recently been developed using curated database(s) of known resistance conferring mutations. However, documenting all the mutations and their effect is a time-taking and a continuous process and therefore Machine Learning (ML) techniques can be useful for predicting the presence of DR-TB based on WGS data. This can pave the way to an earlier detection of drug resistance and consequently more efficient treatment when compared to the traditional DST.

DOI: 10.1016/j.bjid.2022.102332

PMID: 35176257

35. **Estimating tuberculosis drug resistance amplification rates in high-burden settings.**

BMC Infect Dis. 2022 Jan 24;22(1):82. doi: 10.1186/s12879-022-07067-1.

Karmakar M(1)(2)(3), Ragonnet R(4), Ascher DB(1)(2), Trauer JM(4), Denholm JT(5)(6).

BACKGROUND: Antimicrobial resistance develops following the accrual of mutations in the bacterial genome, and may variably impact organism fitness and hence, transmission risk. Classical representation of tuberculosis (TB) dynamics using a single or two strain (DS/MDR-TB) model typically does not capture elements of this important aspect of TB epidemiology. To understand and estimate the likelihood of resistance spreading in high drug-resistant TB incidence settings, we used epidemiological data to develop a mathematical model of Mycobacterium tuberculosis (Mtb) transmission.
METHODS: A four-strain (drug-susceptible (DS), isoniazid mono-resistant (INH-R), rifampicin mono-resistant (RIF-R) and multidrug-resistant (MDR)) compartmental deterministic Mtb transmission model was developed to explore the progression from DS- to MDR-TB in The Philippines and Viet Nam. The models were calibrated using data from national tuberculosis prevalence (NTP) surveys and drug resistance surveys (DRS). An adaptive Metropolis algorithm was used to estimate the risks of drug resistance amplification among unsuccessfully treated individuals.
RESULTS: The estimated proportion of INH-R amplification among failing treatments was 0.84 (95% CI 0.79-0.89) for The Philippines and 0.77 (95% CI 0.71-0.84) for Viet Nam. The proportion of RIF-R amplification among failing treatments was 0.05 (95% CI 0.04-0.07) for The Philippines and 0.011 (95% CI 0.010-0.012) for Viet Nam.
CONCLUSION: The risk of resistance amplification due to treatment failure for INH was dramatically higher than RIF. We observed RIF-R strains were more likely to be transmitted than acquired through amplification, while both mechanisms of acquisition were important contributors in the case of INH-R. These findings highlight the complexity of drug resistance dynamics in high-incidence settings, and emphasize the importance of prioritizing testing algorithms which allow for early detection of INH-R.

DOI: 10.1186/s12879-022-07067-1
PMCID: PMC8785585

PMID: 35073862 [Indexed for MEDLINE]

36. **Improving outcomes for multidrug-resistant TB treatment.**

Int J Tuberc Lung Dis. 2022 Feb 1;26(2):93-95. doi: 10.5588/ijtld.21.0683.

Silva DR(1), de Queiroz Mello FC(2).

DOI: 10.5588/ijtld.21.0683
PMID: 35086619

37. **Hematologic Toxicity of Linezolid in Multidrug Resistant and Extensively Drug Resistant Tuberculosis (MDR/XDR-TB): the role of mitochondria.**

Tuberc Respir Dis (Seoul). 2022 Jan 20. doi: 10.4046/trd.2021.0122. Online ahead of print.

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

Multidrug-resistant tuberculosis (MDR-TB) is resistant to both rifampicin and isoniazid. Extensively drug-resistant TB (XDR-TB) is a rare type of MDR-TB which is resistant to quinolone and one of the group A TB drugs, i.e., linezolid or bedaquiline. In 2018, the World Health Organization revised the groupings of TB medicines and reclassified linezolid as a group A drug for the treatment of MDR-TB. Linezolid is a synthetic antimicrobial agent in the oxazolidinone class. Although linezolid has good efficacy, it can cause substantial adverse events, especially hematologic toxicity. In both TB infection and linezolid mechanism of action, mitochondrial dysfunction plays an important role. In this concise review, linezolid characteristics as an antiTB drug are summarized, including its efficacy; pathogenesis of hematologic toxicity, highlighting mitochondrial dysfunction; and the monitoring and management of hematologic toxicity.

DOI: 10.4046/trd.2021.0122
PMID: 35045688

38. **Identification of thiophene-benzenesulfonamide derivatives for the treatment of multidrug-resistant tuberculosis.**

Eur J Med Chem. 2022 Jan 22;231:114145. doi: 10.1016/j.ejmech.2022.114145. Online ahead of print.

Qin R(1), Wang P(1), Wang B(2), Fu L(2), Batt SM(3), Besra GS(3), Wu C(1), Wang Y(1), Huang H(4), Lu Y(5), Li G(6).

A series of thiophene-benzenesulfonamide derivatives was designed and synthesized by exploring the structure-activity relationship of lead compounds 2,3-disubstituted thiophenes 25a and 297F as antituberculosis agents, which displayed potent antimycobacterial activity against drug-susceptible and clinically isolated drug-resistant tuberculosis. In particular, compound 17b, which had improved activity (minimum inhibitory concentration of 0.023 μg/mL) compared with the lead compounds, displayed good intracellular antimycobacterial activity in macrophages with a reduction of 1.29 log10 CFU. A druggability evaluation indicated that compound 17b had favorable hepatocyte stability, low cytotoxicity, and low hERG channel inhibition. Moreover, compound 17b exhibited modest in vivo efficacy in an acute mouse model of tuberculosis. In addition, the molecular docking study elucidated the binding mode of compound 17b in the active site of DprE1. Therefore, compound 17b may be a promising antituberculosis lead for further research.

DOI: 10.1016/j.ejmech.2022.114145
PMID: 35101648

39. **Direct Molecular Detection of Drug-Resistant Tuberculosis from Transported Bio-Safe Dried Sputum on Filter-Paper.**

Curr Microbiol. 2022 Feb 17;79(4):110. doi: 10.1007/s00284-022-02780-1.

Anthwal D(#)(1)(2), Jamwal S(#)(1), Gupta RK(1)(2), Singhal R(3), Verma AK(3), Bhalla M(3), Myneedu VP(3), Sarin R(3), Choudhary S(2), Tyagi JS(4), Haldar S(5)(6).

In 2019, amongst half a million new rifampicin-resistant tuberculosis (TB) cases, 78% were multi drug-resistant TB (MDR-TB). Access to rapid and Universal-Drug susceptibility testing (DST) to patients in remote areas is a major challenge to combat drug-resistant TB. To overcome this challenge, we had recently reported the development of 'TB Concentration & Transport kit' for bio-safe ambient temperature transport of dried sputum on filter-paper (Trans-Filter). The present study was conducted to evaluate the utility of DNA extracted from sputum on Trans-Filter in a Multiplex PCR-based sequencing assay (Mol-DSTseq) for diagnosing drug-resistant TB. The developed Mol-DSTseq assays were standardized on Mycobacterium tuberculosis clinical isolates (n = 98) and further validated on DNA extracted from sputum on Trans-Filter (n = 100). Using

phenotypic DST as gold standard, the Mol-DSTseq assay showed 100% (95% Confidence Interval [CI] 79.4-100%) and 73.3% (95% CI 54.1-87.7%) sensitivity for detecting rifampicin and isoniazid resistance with a specificity of 85.1% (95% CI 66.2-95.8%) and 100% (95% CI:82.3-100%), respectively. For fluoroquinolones and aminoglycosides, the Mol-DSTseq assay showed a sensitivity of 78.5% (95% CI 49.2-95.3%) and 66.6% (95% CI 9.4-99.1%) with a specificity of 88.2% (95% CI 72.5-96.7%) and 100% (95% CI 93.1-100%), respectively. The Mol-DSTseq assays exhibited a high concordance of ~ 83-96% (κ value: 0.65-0.81) with phenotypic DST for all drugs. In conclusion, the 'TB Concentration and Transport kit' was compatible with Mol-DSTseq assays and has the potential to provide 'Universal-DST' to patients residing in distant areas in high burden countries, like India for early initiation of anti-tubercular treatment.

DOI: 10.1007/s00284-022-02780-1
PMID: 35175411

40. **Draft Genome Sequences of 77 Endemic Multidrug-Resistant Mycobacterium tuberculosis Strains of SIT41 (TUR) Spoligotype from Bulgaria.**

Microbiol Resour Announc. 2022 Feb 17;11(2):e0111121. doi: 10.1128/mra.01111-21. Epub 2022 Feb 10.

Panaiotov S(1), Tolchkov V(1), Hodzhev Y(1), Tsafarova B(1), Trovato A(2), Cirillo D(2).

Sequences of multidrug-resistant (MDR) Mycobacterium tuberculosis strains are of particular interest to study the molecular mechanisms of drug resistance evolution. Here, we report the draft genome sequences of 77 endemic multidrug-resistant Mycobacterium tuberculosis strains of SIT41 (TUR) spoligotype from Bulgaria. SIT41 spoligotype is dominant (>40%) among the MDR-TB strains in Bulgaria.

DOI: 10.1128/mra.01111-21
PMCID: PMC8830331
PMID: 35142538

41. **All-oral longer regimens are effective for the management of multidrug-resistant tuberculosis in high-burden settings.**

Eur Respir J. 2022 Jan 20;59(1):2004345. doi: 10.1183/13993003.04345-2020. Print 2022 Jan.

Khan PY(1)(2)(3), Franke MF(4)(5)(3), Hewison C(6), Seung KJ(4)(7), Huerga H(8), Atwood S(7), Ahmed S(9), Khan M(10), Sultana T(11), Manzur-Ul-Alam M(11), Vo LNQ(12)(13), Lecca L(14), Yae K(15), Kozhabekov S(16), Tamirat M(17), Gelin A(18), Vilbrun SC(19), Kikvidze M(20), Faqirzai J(21), Kadyrov A(22), Skrahina A(23), Mesic A(24), Avagyan N(6), Bastard M(8), Rich ML(4)(7), Khan U(12)(3), Mitnick CD(4)(5)(3).

BACKGROUND: Recent World Health Organization guidance on drug-resistant tuberculosis treatment de-prioritised injectable agents, in use for decades, and endorsed all-oral longer regimens. However, questions remain about the role of the injectable agent, particularly in the context of regimens using new and repurposed drugs. We compared the effectiveness of an injectable-containing regimen to that of an all-oral regimen among patients with drug-resistant tuberculosis who received bedaquiline and/or delamanid as part of their multidrug regimen.
METHODS: Patients with a positive baseline culture were included. 6-month culture conversion was defined as two consecutive negative cultures collected >15 days apart. We derived predicted probabilities of culture conversion and relative risk using marginal standardisation methods.
RESULTS: Culture conversion was observed in 83.8% (526 out of 628) of patients receiving an all-oral regimen and 85.5% (425 out of 497) of those receiving an injectable-containing regimen. The adjusted relative risk comparing injectable-containing regimens to all-oral regimens was 0.96 (95% CI 0.88-1.04). We found very weak evidence of effect modification by HIV status: among patients living with HIV, there was a small increase in the frequency of conversion among those receiving an injectable-containing regimen, relative to an all-oral regimen, which was not apparent in HIV-negative patients.
CONCLUSIONS: Among individuals receiving bedaquiline and/or delamanid as part of a multidrug regimen for drug-resistant tuberculosis, there was no significant difference between those who received an injectable and those who did not regarding culture conversion within 6 months. The potential contribution of injectable agents in the treatment of drug-resistant tuberculosis among those who were HIV positive requires further study.

DOI: 10.1183/13993003.04345-2020
PMID: 34140298 [Indexed for MEDLINE]

42. **Evaluation of Mobile Application for the Management of Tuberculosis Patients in Tianjin During 2019-2020.**

Patient Prefer Adherence. 2022 Feb 9;16:321-329. doi: 10.2147/PPA.S321289. eCollection 2022.

Li X(1), Pang X(1), Zhang F(1).

PURPOSE: Poor tuberculosis (TB) medication adherence increases the risk of treatment failure and development of drug-resistant TB, while universal implementation of directly observed therapy (DOT) is not feasible in China. EHealth technologies were reported to be promising patient-centered tools for improving adherence. However, only pilot studies have assessed patients' experiences, and the results were discrepant.
PATIENTS AND METHODS: This prospective-cohort study was conducted among TB patients at the outpatient department from 3 March 2019 to 30 May 2020 in Tianjin, China. Data were downloaded from the Tuberculosis Doctor App and TB Information Management System (TBIMS) and merged them by the TBIMS notification number. Logistic regression analysis was used to analyze the factors associated with regular drug-intake. Odds ratios and 95% confidence intervals were estimated with and without adjustment for age, gender, ethnicity and occupation.
RESULTS: Revisit examination was more regularly and frequently in APP group than non-APP group. In APP group, 33.28% patients were regular drug-intake. The whole drug-intake rate was 84.84%. Tuberculosis pleurisy (aOR: 0.42, 95CI%=0.26-0.69) and retreated patients (aOR: 0.40, 95CI% =0.27-0.59) were more likely to have poor medication compliance. Local residents tend to have better medication compliance (aOR: 1.80, 95CI% =1.16-2.79).
CONCLUSION: APP could improve TB patients' revisit examination adherence. Medication adherence was poor in tuberculosis pleuritis and retreated patients, while local residents tend to have better medication adherence. To make full use of the mobile application in TB patient management, more incentive measures should be adopted for patients and doctors, respectively.

DOI: 10.2147/PPA.S321289
PMCID: PMC8841537
PMID: 35173417

43. **Effect of Mixed Infections with Mycobacterium tuberculosis and Nontuberculous Mycobacteria on Diagnosis of Multidrug-Resistant Tuberculosis: A Retrospective Multicentre Study in China.**

Infect Drug Resist. 2022 Jan 20;15:157-166. doi: 10.2147/IDR.S341817.
eCollection 2022.

Huang M(#)(1), Tan Y(#)(2), Zhang X(#)(3), Wang Y(3), Su B(2), Xue Z(3), Wang J(4), Pang Y(3).

BACKGROUND: Correct species identification is essential before initiation of TB treatment, due to substantial drug susceptibility profile differences among mycobacterial species. Given that nontuberculous mycobacteria (NTM) are frequently resistant to first-line anti-tuberculosis drugs, cases with mixed infections with Mycobacterium tuberculosis (MTB) and NTM tend to be diagnosed as multidrug-resistant tuberculosis (MDR-TB) cases. Here we report results of a retrospective multicentre study that was conducted to determine the prevalence of TB-NTM infections in previously diagnosed laboratory-confirmed multidrug-resistant tuberculosis (MDR-TB) patients using phenotypic drug susceptibility testing. The results were then used to identify risk factors associated with susceptibility to mixed infections.
METHODS: From January 2019 through December 2019, we retrospectively collected MDR-TB isolates from three TB specialised hospitals. Species identifications of isolates were performed using the MeltPro Myco assay.
RESULTS: A total of 837 MDR-TB isolates were analysed, of which 22 isolates (2.6%) were found to contain a mixture of NTM and MTB organisms. Significant differences in prevalence rates of mixed infections across regions were observed, with prevalence rates ranging from 0.0% (0/213) in Beijing to 3.4% (12/353) in Fuzhou to 3.7% (10/271) in Guangzhou. Among the 22 patients with NTM-TB mixed infections, a total of five different mycobacterial species were identified, of which the most prevalent species was Mycobacterium intracellulare. Notably, a history of previous TB episodes correlated with higher mixed infection risk.
CONCLUSION: The results reported here demonstrated that mixed infections with MTB and NTM occurred in approximately 3% of suspected MDR-TB patients in China. These findings raise concerns about the accuracy of molecular diagnostics-based species identification tests and draw attention to the possibility that NTM-MTB mixed infections will be misdiagnosed as MDR-TB in high TB burden settings.

DOI: 10.2147/IDR.S341817
PMCID: PMC8786360
PMID: 35082503

44. **Xpert MTB/RIF Improves the Prognosis of Multidrug-Resistant Tuberculosis Patients Through Faster Diagnosis and Earlier Targeted Treatment: A Prospective**

Cohort Study.

Microb Drug Resist. 2022 Feb 11. doi: 10.1089/mdr.2021.0149. Online ahead of print.

Shi JC(1), Wang X(2), Huang RS(3), Ning HY(1), Cai YW(1), Wu LP(4), Liu SD(1), Wu ZX(1), Zhou YY(1), Zheng Y(3), Jiang XG(1).

Objective: To evaluate the effectiveness of Xpert MTB/RIF in patients with multidrug-resistant tuberculosis (MDR-TB). Methods: Seventy-five patients with MDR-TB were enrolled in this prospective cohort study and were divided into two groups. The observation group were given standardized anti-MDR-TB treatment regimen (6ZAmLfxPtoCs/18ZLfxPtoCs) immediately when they had two positive sputum Xpert MTB/RIF results of RIF resistance. The control group were not given standardized anti-MDR-TB regimen until culture-based drug-susceptibility testing suggested MDR-TB. Treatment effect index, foci absorption, conversion of sputum, treatment outcomes, and adverse reactions were observed. Fisher's exact test and chi-square test were used to compare the differences between groups. Results: Treatment effect index of the observation group significantly out-performed the control group (24/34, 70.6% vs. 17/38, 44.7%, p = 0.027). At the 6th month of treatment course, observation group achieved significantly higher conversion (28/34, 82.3% vs. 23/38, 60.5%, p = 0.042). The foci absorption, cavity change, conversion at the 24th month of course, or treatment outcome between two groups were not statistically different. Conclusion: Xpert MTB/RIF helps MDR-TB patients to start rational treatment regimen earlier and reach earlier sputum conversion.

DOI: 10.1089/mdr.2021.0149
PMID: 35148485

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

Lancet Infect Dis. 2022 Feb;22(2):156-157. doi: 10.1016/S1473-3099(21)00481-3. Epub 2021 Oct 7.

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

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

46. **Developing a patient-centered community-based model for management of multi-drug**

resistant tuberculosis in Uganda: a discrete choice experiment.

BMC Health Serv Res. 2022 Feb 5;22(1):154. doi: 10.1186/s12913-021-07365-5.

Makabayi-Mugabe R(1)(2), Musaazi J(3), Zawedde-Muyanja S(3)(4), Kizito E(4), Namwanje H(4), Aleu P(4), Charlet D(5), Freitas Lopez DB(5), Brightman H(5), Turyahabwe S(6), Nkolo A(4).

BACKGROUND: The advent of all-oral regimens for the management of multi-drug resistant tuberculosis (MDR-TB) makes the implementation of community-based directly observed therapy (CB-DOT) a possibility for this group of patients. We set out to determine patient preferences for different attributes of a community-based model for the management of MDR-TB in Uganda.
METHODS: The study was conducted at five tertiary referral hospitals. We used a parallel convergent mixed methods study design. To collect quantitative data, we conducted a discrete choice experiment (DCE) with three different attributes of community-based care (DOT provider, location of care, and type of support) combined into eight choice sets, each with two options and an opt-out. We elicited patient reasons for selection of each choice set using qualitative methods. We fitted a mixed logit choice model to determine patient preferences for different attributes of community-based care and estimated the relative importance of each attribute using the range method. and used deductive thematic analysis to understand the reasons for the choices made.
RESULTS: From December 2019 to January 2020, we interviewed 103 patients with MDR-TB. We found that all the three attributes considered were important predicators of choice. The relative importance of each attribute was as follows; the type of additional support (relative importance 36.2%), the location of treatment delivery (33.5%), and the type of DOT provider (30.3%). Participants significantly valued treatment delivered by community health workers (CHWs) or expert clients over that delivered by a family member, treatment delivered at home over that delivered at the workplace, and monthly travel vouchers as the form of additional support over phone call or SMS reminders. Subgroup analyses showed significant differences in preference across HIV status, age groups and duration on MDR-TB treatment, but not across gender. The preferred model consisted of a CHW giving DOT at home and travel vouchers to enable attendance of monthly clinic follow-up visits to tertiary referral hospitals for treatment monitoring. Qualitative interviews revealed that patients perceived CHWs as knowledgeable and able to offer psychosocial support. Patients also preferred to take medication at home to save both time and money and lower the risk of facing TB stigma.
CONCLUSION: People with MDR-TB prefer to be supported to take their medicine at home by a member of their community. The effectiveness of this model of care is being further evaluated.

DOI: 10.1186/s12913-021-07365-5
PMCID: PMC8817775
PMID: 35123467 [Indexed for MEDLINE]

47. **A qualitative study of patients and healthcare workers' experiences and perceptions to inform a better understanding of gaps in care for pre-discharged tuberculosis patients in Cape Town, South Africa.**

BMC Health Serv Res. 2022 Jan 29;22(1):128. doi: 10.1186/s12913-022-07540-2.

Kallon II(1)(2), Colvin CJ(3)(4)(5), Trafford Z(3)(6).

BACKGROUND: Many people diagnosed with Mycobacterium tuberculosis (TB) in tertiary and district hospitals in South Africa do not arrive at their primary care clinic for continued care after they are discharged from the hospital. This loss to follow up is a major, ongoing problem for public health in South Africa, and contributes to drug-resistant TB strains. The objective of this paper was to explore patients' experiences and perceptions of diagnosis and treatment before their discharge from hospital. We use a framework known as patient-centred care to illustrate how these patient narratives point to lapses in these principles within the hospital system, and to show how such lapses may contribute to loss to follow up and inconsistent TB care.
METHODS: We employed a qualitative study using semi-structured interviews to investigate patient and healthcare workers' experiences and perceptions of TB care in two Western Cape hospitals. We purposefully sampled 17 patients, 10 healthcare workers, and two key informant policy makers, all of whom had relevant experiences and insights. Data collection was done between October 2015 and February 2017. Data were analysed using Miles and Huberman's qualitative analysis framework.
RESULTS: Hospitals did not achieve patient-centred care. Newly diagnosed patients were provided with inadequate TB education, diseased-focused approaches were favoured over patient-focused approaches, and there was limited engagement with patients to understand their needs and feelings during the critical period between diagnosis and discharge. Consequently, some patients felt anxious prior to their discharge from hospital. Coupled with their overwhelming socio-economic barriers and complex family situations, some patients felt hopeless and powerless as they prepared for discharge. Finally, there was a lack of patient-provider partnership due to problems including healthcare workers' time constraints and heavy workloads, which detracted from a focus on patients' needs and feelings.
CONCLUSIONS: Improving the three intersecting elements of patient-centred care

(health education, engaging with patients' needs and feelings, and shared decision-making) has the potential to positively influence patients' continuity of care for TB in South Africa. It would be helpful to also proactively address how patients plan to stay connected to care, on treatment, and supported, in light of their family situation or socio-economic circumstances. Detailed and unique pre-discharge counselling for each patient may be valuable in this regard.

DOI: 10.1186/s12913-022-07540-2
PMCID: PMC8801106
PMID: 35093053 [Indexed for MEDLINE]

48. **Significance of the coexistence of non-codon 315 katG, inhA, and oxyR-ahpC intergenic gene mutations among isoniazid-resistant and multidrug-resistant isolates of Mycobacterium tuberculosis: a report of novel mutations.**

Pathog Glob Health. 2022 Feb;116(1):22-29. doi: 10.1080/20477724.2021.1928870. Epub 2021 Jun 4.

Norouzi F(1), Moghim S(1), Farzaneh S(1), Fazeli H(1), Salehi M(2), Nasr Esfahani B(1).

Tuberculosis (TB) is a global threat due to the emergence and spread of drug-resistant Mycobacterium tuberculosis (MTB). Isoniazid (INH) is the main antibiotic used for prevention and treatment of TB. Evidence shows that accumulated mutations can produce INH resistant (INHR) strains, resulting in the progression of multidrug-resistant (MDR) TB. Since point mutations in katG gene, inhA gene, and oxyR-ahpC region correlated with the INH resistance, in this study, we aimed to identify mutations in these three genes in INHR and MDR clinical isolates of MTB by Sanger DNA sequencing analysis. Thirty-three out of 438 isolates were resistant, including 66.7% INHR and 30.3% MDR isolates. In the katG gene, 68.2% INHR isolates had non-synonymous point mutations, mainly R463L (63.6%), and non-synonymous point mutation KatG L587P was seen in one of the MDR isolate. A novel silent substitution L649L was identified in the inhA gene of the MDR isolates. The oxyR-ahpC intergenic region g-88a common mutations (63.6%) in INHR and two distinct novel mutations were found at positions -76 and -77 of the oxyR-ahpC intergenic region. The coexistence of katG non-codon 315 with oxyR-ahpC intergenic region mutations was highly frequent in INHR 59.1% and MDR isolates 70%. Since mutations of all three genes 95.5% lead to the detection of INHR, they might be useful for molecular detection. Our results indicated the continuous evolution and region-specific prevalence of INH resistance. Overall,

identification of new mutations in INH resistance can improve the available strategies for diagnosis and control of TB.

DOI: 10.1080/20477724.2021.1928870
PMCID: PMC8812758
PMID: 34086544

49. **Increased Moxifloxacin Dosing Among Patients With Multidrug-Resistant Tuberculosis With Low-Level Resistance to Moxifloxacin Did Not Improve Treatment Outcomes in a Tertiary Care Center in Mumbai, India.**

Open Forum Infect Dis. 2021 Dec 23;9(2):ofab615. doi: 10.1093/ofid/ofab615. eCollection 2022 Feb.

Tornheim JA(1), Udwadia ZF(2), Arora PR(3), Gajjar I(3), Sharma S(3), Karane M(3), Sawant N(3), Kharat N(3), Blum AJ(4), Shivakumar SVBY(5), Gupte AN(1), Gupte N(1)(5), Mullerpattan JB(2), Pinto LM(2), Ashavaid TF(3), Gupta A(1)(6), Rodrigues C(7).

BACKGROUND: Mycobacterium tuberculosis (Mtb) strains resistant to isoniazid and rifampin (multidrug-resistant tuberculosis [MDR-TB]) are increasingly reported worldwide, requiring renewed focus on the nuances of drug resistance. Patients with low-level moxifloxacin resistance may benefit from higher doses, but limited clinical data on this strategy are available.
METHODS: We conducted a 5-year observational cohort study of MDR-TB patients at a tertiary care center in India. Participants with Mtb isolates resistant to isoniazid, rifampin, and moxifloxacin (at the 0.5 μg/mL threshold) were analyzed according to receipt of high-dose moxifloxacin (600 mg daily) as part of a susceptibility-guided treatment regimen. Univariable and multivariable Cox proportional hazard models assessed the relationship between high-dose moxifloxacin and unfavorable treatment outcomes.
RESULTS: Of 354 participants with MDR-TB resistant to moxifloxacin, 291 (82.2%) received high-dose moxifloxacin. The majority experienced good treatment outcomes (200 [56.5%]), which was similar between groups (56.7% vs 54.0%, P = .74). Unfavorable outcomes were associated with greater extent of radiographic disease, lower initial body mass index, and concurrent treatment with fewer drugs with confirmed phenotypic susceptibility. Treatment with high-dose moxifloxacin was not associated with improved outcomes in either unadjusted (hazard ratio [HR], 1.2 [95% confidence interval {CI}, .6-2.4]) or adjusted (HR, 0.8 [95% CI, .5-1.4]) models but was associated with joint pain (HR, 3.2 [95% CI, 1.2-8.8]).
CONCLUSIONS: In a large observational cohort, adding high-dose (600 mg) moxifloxacin to a drug susceptibility test-based treatment regimen for MDR-TB

was associated with increased treatment-associated side effects without improving overall outcomes and should be avoided for empiric treatment of moxifloxacin-resistant MDR-TB.

DOI: 10.1093/ofid/ofab615
PMCID: PMC8794589
PMID: 35097152

50. **Telacebec: an investigational antibacterial for the treatment of tuberculosis (TB).**

Expert Opin Investig Drugs. 2022 Jan 26:1-6. doi: 10.1080/13543784.2022.2030309. Online ahead of print.

Lee BS(1), Pethe K(1)(2).

INTRODUCTION: Tuberculosis is an infectious disease that affected more than 50 million people and killed 6.7 million patients in the past 5 years alone. Additionally, rising incidence of treatment resistance threatens the global effort to eradicate this disease. With limited options available, additional novel antibiotics are needed for the treatment of multidrug-resistant tuberculosis (MDR-TB). Telacebec is a first-in-class antibiotic that targets the pathogen's energy metabolism.
AREAS COVERED: This paper provides an overview of the recent progress in the development and testing of telacebec. We discuss published clinical data and examine the design and setup of its clinical trials. We also offer insights on the therapeutic potential of telacebec and aspects of which should be evaluated in the future.
EXPERT OPINION: The first phase 2a trial showed a correlation between dosage and bacterial load in patient sputum, which should be confirmed using a direct measurement method such as colony-forming unit counting. Its clinical efficacy, favorable pharmacokinetic properties, low arrhythmogenic risk, and activity against MDR-TB strains make telacebec a suitable candidate for further development. Future clinical testing in combination with approved second-line drugs will reveal its full potential against MDR-TB. Considering recent preclinical studies, we also recommend initiating clinical trials for Buruli ulcer and leprosy.

DOI: 10.1080/13543784.2022.2030309
PMID: 35034512

51. **Chrysomycin A inhibits the topoisomerase I of Mycobacterium tuberculosis.**

J Antibiot (Tokyo). 2022 Feb 8. doi: 10.1038/s41429-022-00503-z. Online ahead of print.

Muralikrishnan B(1), Edison LK(1), Dusthackeer A(2), Jijimole GR(1), Ramachandran R(1), Madhavan A(1), Kumar RA(3).

Novel anti-tuberculosis drugs are essential to manage drug-resistant tuberculosis, caused by Mycobacterium tuberculosis. We recently reported the antimycobacterial activity of chrysomycin A in vitro and in infected macrophages. In this study, we report that it inhibits the growth of drug-resistant clinical strains of M. tuberculosis and acts in synergy with anti-TB drugs such as ethambutol, ciprofloxacin, and novobiocin. In pursuit of its mechanism of action, it was found that chrysomycin A is bactericidal and exerts this activity by interacting with DNA at specific sequences and by inhibiting the topoisomerase I activity of M. tuberculosis. It also exhibits weak inhibition of the DNA gyrase enzyme of the pathogen.

DOI: 10.1038/s41429-022-00503-z
PMID: 35136191

52. **Epidemiological Characteristics and Their Influencing Factors Among Pulmonary Tuberculosis Patients With and Without Diabetes Mellitus: A Survey Study From Drug Resistance Surveillance in East China.**

Front Public Health. 2022 Jan 24;9:777000. doi: 10.3389/fpubh.2021.777000. eCollection 2021.

Wu Q(1), Wang M(2), Zhang Y(1), Wang W(1), Ye TF(3), Liu K(1), Chen SH(1).

BACKGROUND: The burden of pulmonary tuberculosis (TB) and diabetes mellitus (DM) have become serious global concerns, while the comprehensive evaluations of DM status and drug resistance in TB patients are still lacking.
METHODS: All details of TB cases were collected from drug resistance monitoring sentinels in Zhejiang province. Fisher's exact test or Pearson chi-square test ($\chi 2$) was used to compare the baseline characteristics among TB with different DM statuses. The logistic regression model was used to estimate the relationship

between DM and different drug resistance spectra. Univariate analysis and multivariate logistic model were used to explore the possible risk factors of drug resistance in TB patients with DM and no DM.
RESULTS: 936 TB cases with smear-positive in Zhejiang province were collected, in which 76 patients (8.12%) owned the co-morbidity of DM. TB-DM prevalence was higher in older, Han nationality, employed, accompanied by no health insurance and hepatitis B status. Among 860 cases of TB-no DM and 76 cases of TB-DM, drug resistance-TB accounted for 31.51% and 23.68% ($P > 0.05$), MR-TB accounted for 15.93% and 14.47% ($P > 0.05$), respectively. MDR-TB was 4.88% and 6.58% ($P > 0.05$). The incidence of poly-drug resistant tuberculosis (PDR-TB) in TB-no DM patients (10.70 vs. 2.63%, OR: 4.43; 95% CI, 1.07-18.36) was higher than that in the TB-DM group ($P < 0.05$). In univariate and multivariate analysis, none of the basic factors were statistically significant with drug resistance among TB-DM cases (all $P > 0.05$). Retreatment was the risk factor of drug resistance among TB-no DM cases.
CONCLUSIONS: Our results showed that the drug resistance rate of the TB-DM group was not higher than that of the TB-no DM group. Patients with TB-no DM were at a higher risk for PDR-TB, but not for MDR-TB, MR-TB, and drug resistance-TB. Special attention should be paid to TB-no DM patients who have been previously treated. In the future, large-scale and well-designed prospective studies are needed to clarify the impact of DM on the drug-resistance among TB.

DOI: 10.3389/fpubh.2021.777000
PMCID: PMC8818727
PMID: 35141185

53. **New silver(I) phosphino complexes: Evaluation of their potential as prospective agents against Mycobacterium tuberculosis.**

J Inorg Biochem. 2022 Feb;227:111683. doi: 10.1016/j.jinorgbio.2021.111683. Epub 2021 Dec 3.

Maldonado YD(1), Scalese G(2), Manieri KF(3), Pavan FR(3), Aguirre Méndez LD(4), Gambino D(5).

Despite being a preventable and curable disease, Tuberculosis (TB) is the world's top infectious killer. Development of new drugs is urgently needed. In this work, the synthesis and characterization of new silver(I) complexes, that include N'-[(E)-(pyridine-2-ylmethylene)pyrazine-2-carbohydrazide, HPCPH, as main ligand and substituted aryl-phosphines as auxiliary ligands, is reported. HPCPH was synthesized from pyrazinoic acid, the active metabolite of the

first-line antimycobacterial drug pyrazinamide. Complexes [Ag(HPCPH)(PPh3)2]OTf (1), [Ag(HPCPH)((P(p-tolyl)3)2]OTf (2) and [Ag(HPCPH)(P(p-anisyl)3)2]OTf (3) were characterized in solid state and in solution by elemental analysis and FTIR and NMR spectroscopies (OTftriflate). Crystal structures of (1,2) were determined by XRD. The Ag atom is coordinated to azomethine and pyridine nitrogen atoms of HPCPH ligand and to the phosphorous atom of each aryl-phosphine co-ligand. Although HPCPH did not show activity, the Ag(I) compounds demonstrated activity against Mycobacterium tuberculosis (MTB), H37Rv strain, and multi-drug resistant clinical isolates (MDR-TB). Globally, results showed that the compounds are not only effective against the sensitive strain, but are more potent against MDR-TB than antimycobacterial drugs used in therapy. The compounds showed low to moderate selectivity index values (SI) towards the bacteria, using MRC-5 cells (ATCC CCL-171) as mammalian cell model. Interaction with DNA was explored to get insight into the potential mechanism of action against the pathogen. No significant interaction was detected, allowing to discard this biomolecule as a potential molecular target. Compound 1 was identified as a hit compound (MIC90 2.23 μM; SI 4.4) to develop further chemical modifications in the search for new drugs.

DOI: 10.1016/j.jinorgbio.2021.111683
PMID: 34896768 [Indexed for MEDLINE]

54. **An All-Oral 6-Month Regimen for Multidrug-Resistant TB (the NExT Study): A Multicenter, Randomized Controlled Trial.**

Am J Respir Crit Care Med. 2022 Feb 17. doi: 10.1164/rccm.202107-1779OC. Online ahead of print.

Esmail A(1)(2), Oelofse S(3)(2), Lombard C(4)(5), Perumal R(3)(2), Mbuthini L(3), Goolam Mahomed A(6), Variava E(7)(8), Black J(9), Oluboyo P(10), Gwentshu N(11), Ngam E(11), Ackerman T(12), Marais L(13), Mottay L(3)(2), Meier S(14)(2), Pooran A(3)(2), Tomasicchio M(3)(15), Te Riele J(16), Derendinger B(17), Ndjeka N(18), Maartens G(19), Warren R(20), Martinson N(21)(22), Dheda K(23)(2)(24).

Rationale/objectives: Improving treatment outcomes, reducing drug toxicity, avoiding injectable agents, and shortening the treatment duration to 6-months (approximating that of rifampicin-susceptible tuberculosis) remains an aspirational goal for the treatment of multidrug-resistant/rifampicin-resistant tuberculosis (MDR/RR-TB).
METHODS: We conducted a multicentre randomised controlled trial in adults with MDR/RR-TB (i.e. without resistance to fluoroquinolones or aminoglycosides).

Participants were randomly assigned (1:1 ratio) to a ~6-month all-oral regimen that included levofloxacin, bedaquiline and linezolid, or the standard-of-care ≥ 9-month WHO-approved injectable-based regimen. The primary endpoint was a favourable WHO-defined treatment outcome 24 months after treatment initiation.
MAIN RESULTS: 93 of 111 participants randomised were included in the modified intention-to-treat analysis; 51 (55%) were HIV co-infected (median CD4 count 158 cells/mL). Participants in the intervention arm were 2.2 times more likely to experience a favourable 24-month outcome than participants in the standard-of-care arm [RR 2.2 (1.2-4.1); p=0.006]. Toxicity-related drug substitution occurred more frequently in the standard-of-care arm [(65·9% (29/44) versus 36·7% (18/49), p= 0·001)]; 79.3% (23/29) due to kanamycin (mainly hearing loss; replaced by bedaquiline) in the standard-of-care arm, and 83·3% (15/18) due to linezolid (mainly anaemia) in the interventional arm. Culture conversion was significantly better in the intervention arm [HR 2.6 (1.4-4.9); p= 0.003] after censoring those with bedaquiline replacement in the standard-of-care arm.
CONCLUSIONS: An all-oral 6-month levofloxacin, bedaquiline and linezolid-containing MDR/RR-TB regimen was associated with significantly improved 24-month treatment outcomes compared with traditional injectable-containing regimens. However, drug toxicity occurred frequently in both arms. These findings inform strategies to develop future regimens for MDR/RR-TB. Clinical trial registration available at www.clinicaltrials.gov, ID: NCT02454205.

DOI: 10.1164/rccm.202107-1779OC
PMID: 35175905

55. **Probing the Molecular Basis of Cofactor Affinity and Conformational Dynamics of Mycobacterium tuberculosis Elongation Factor Tu: An Integrated Approach Employing Steered Molecular Dynamics and Umbrella Sampling Simulations.**

J Phys Chem B. 2022 Feb 15. doi: 10.1021/acs.jpcb.1c09438. Online ahead of print.

Kumar N(1), Garg P(1).

The emergence of multidrug-resistant and extensively drug-resistant tuberculosis strains is the reason that the infectious tuberculosis pathogen is still the most common cause of death. The quest for new antitubercular drugs that can fit into multidrug regimens, function swiftly, and overcome the ever-increasing prevalence of drug resistance continues. The crucial role of MtbEF-Tu in translation and trans-translation processes makes it an excellent target for antitubercular drug design. In this study, the primary sequence of MtbEF-Tu was

used to model the three-dimensional structures of MtbEF-Tu in the presence of GDP ("off" state) and GTP ("on" state). The binding free energy computed using both the molecular mechanics/Poisson-Boltzmann surface area and umbrella sampling approaches shows that GDP binds to MtbEF-Tu with an ∼2-fold affinity compared to GTP. The steered molecular dynamics (SMD) and umbrella sampling simulation also shows that the dissociation of GDP from MtbEF-Tu in the presence of Mg2+ is a thermodynamically intensive process, while in the absence of Mg2+, the destabilized GDP dissociates very easily from the MtbEF-Tu. Naturally, the dissociation of Mg2+ from the MtbEF-Tu is facilitated by the nucleotide exchange factor EF-Ts, and this prior release of magnesium makes the dissociation process of destabilized GDP easy, similar to that observed in the umbrella sampling and SMD study. The MD simulations of MtbEF-Tu's "on" state conformation in the presence of GTP reveal that the secondary structure of switch-I and Mg2+ coordination network remains similar to its template despite the absence of identity in the conserved region of switch-I. On the other hand, the secondary structure in the conserved region of the switch-I of MtbEF-Tu unwinds from a helix to a loop in the presence of GDP. The major conformational changes observed in switch-I and the movement of Thr64 away from Mg2+ mainly reflect essential conformational changes to make the shift of MtbEF-Tu's "on" state to the "off" state in the presence of GDP. These obtained structural and functional insights into MtbEF-Tu are pivotal for a better understanding of structural-functional linkages of MtbEF-Tu, and these findings may serve as a basis for the design and development of MtbEF-Tu-specific inhibitors.

DOI: 10.1021/acs.jpcb.1c09438
PMID: 35167282

56. **Microwave-assisted organic synthesis, antimycobacterial activity, structure-activity relationship and molecular docking studies of some novel indole-oxadiazole hybrids.**

SAR QSAR Environ Res. 2022 Feb;33(2):89-109. doi: 10.1080/1062936X.2022.2032333. Epub 2022 Feb 1.

Desai NC(1), Somani HC(1), Mehta HK(1), Jadeja DJ(1), Khasiya AG(1), Khedkar VM(2).

Multidrug-resistant tuberculosis (MDR-TB) is a severe threat to mankind because most drugs are ineffective in inhibiting tubercular strains. Due to the increase of MDR-TB, many first and second-line drugs are ineffective against tubercular strains. To combat the resistance of currently accessible drugs, structural changes must be made on a regular basis. Thus, in the search for new antimycobacterial drugs, a series of

1-(2-(1H-indol-3-yl)-5-phenyl-1,3,4-oxadiazol-3(2H)-yl)-3-phenylprop-2-en-1-ones (5a-o) have been developed, synthesized, characterized, and screened for antimycobacterial activity. The synthetic approach includes imine generation and cyclization using both conventional and microwave methods to create hybrid molecules with indole and oxadiazole motifs. The set of synthesized compounds have demonstrated some promising activity against tubercular strains of Mycobacterium tuberculosis (ATCC 25177) and M. bovis (ATCC 35734). Compound 5l inhibited M. bovis strain 100% in 10 µg/mL concentration, while compound 5m inhibited M. tuberculosis strain 90.4% in 30 µg/mL concentration. Molecular docking study against mycobacterial enoyl reductase (InhA) could provide well-clustered solutions to the binding modes and affinity for these molecules as compound 5l showed glide score of -12.275 and glide energy of -54.937 kcal/mol.

DOI: 10.1080/1062936X.2022.2032333
PMID: 35102805 [Indexed for MEDLINE]

57. **Frequent Suboptimal Thermocycler Ramp Rate Usage Negatively Impacts GenoType MTBDRsl VER 2.0 Performance for Second-Line Drug-Resistant Tuberculosis Diagnosis.**

J Mol Diagn. 2022 Jan 31:S1525-1578(22)00013-7. doi: 10.1016/j.jmoldx.2022.01.003. Online ahead of print.

Derendinger B(1), de Vos M(1), Pillay S(1), Venter R(1), Metcalfe J(2), Ghebrekristos Y(3), Minnies S(1), Dolby T(4), Beylis N(4), Warren R(1), Theron G(5).

Strengthening detection of second-line drug-resistant tuberculosis (TB) is a priority. The performance of GenoType MTBDRplus VER 2.0 for multidrug resistance is reduced when nonrecommended ramp rates (temperature change speed between PCR cycles) are used. The effect of ramp rates on the performance of GenoType MTBDRsl VER 2.0 (MTBDRsl), a widely used second-line drug-resistant TB assay, was investigated. Fifty-two Xpert MTB/RIF Ultra-positive rifampicin-resistant smear-negative sputa and a Mycobacterium tuberculosis dilution series were tested at a manufacturer-recommended (2.2°C/second) or suboptimal (4.0°C/second) ramp rate. M tuberculosis-complex-DNA positivity, indeterminates, fluoroquinolone- and second-line injectable-resistance accuracy, banding differences, and, separately, inter-reader variability were assessed. Five (39%) of 13 re-surveyed laboratories did not use the manufacturer-recommended ramp rate. On sputa, 2.2°C/second improved indeterminates versus 4.0°C/second (0 of 52 versus 7 of 51; P = 0.006), incorrect drug-class diagnostic calls (0 of 104 versus 6 of 102; P = 0.013), and incorrect banding calls (0 of 1300 versus 54 of

1275; P < 0.001). On sputa, the optimal ramp rate improved valid results [neither M tuberculosis-complex-DNA-negative, indeterminate, nor any false drug-resistance calls) [52 of 52 versus 41 of 51; 21% (95% CI, 8-34; P = 0.001) improved] and banding call inter-reader variability [34 of 1300 (3%) versus 52 of 1300 (4%); P = 0.030]. At the suboptimal ramp rate, false-resistance and false-susceptible calls resulted from probes not binding rather than mutant bands appearing. This also resulted in moxifloxacin resistance misclassification level from high to low. A suboptimal ramp rate contributes to poor MTBDRsl performance. Ramp rate correction will improve second-line drug-resistant TB. Laboratories must ensure that the manufacturer-recommended ramp rate is used.

DOI: 10.1016/j.jmoldx.2022.01.003
PMID: 35108607

58. **Phytochemical screening, antimycobacterial activity and acute toxicity of crude extracts of selected medicinal plant species used locally in the treatment of tuberculosis in Uganda.**

Trop Med Health. 2022 Feb 17;50(1):16. doi: 10.1186/s41182-022-00406-7.

Oloya B(1)(2), Namukobe J(3), Ssengooba W(4), Afayoa M(5), Byamukama R(3).

BACKGROUND: Tuberculosis (TB) is one of the leading causes of death globally, and the rise in drug-resistant forms of TB has become a significant threat. Subsequently, it is crucial to explore new, effective and safe anti-TB agents. This study aimed at conducting phytochemical screening, antimycobacterial activity, and acute toxicity of the selected plant species' crude extracts to assess their toxicological potentials and efficacies against TB.
METHODS: The aqueous and methanol/dichloromethane (DCM) (1:1) extracts of each selected plant species were subjected to phytochemical screening and antimycobacterial activity using microplate alamar blue assay. For acute toxicity, a single dose (2000 mg/kg) of the aqueous extracts was orally administered to each animal following the Organization for Economic Cooperation and Development (OECD) guidelines No. 425 and then observed for 14 days. The animals were closely observed on the general behavior and clinical signs of toxicity, and body weights were recorded. After the termination of the experiment, hematological, biochemical, and histopathological analyses were performed.
RESULTS: The extracts contained alkaloids, flavonoids, tannins, saponins, steroids, terpenoids, resins, cardiac glycosides, phenolic compounds, and

coumarins. Aqueous extracts showed moderate to weak activity against the susceptible (H37Rv) M. tuberculosis strain and weak activity against the MDR-TB strain with Minimum Inhibitory Concentrations (MIC μg/mL) ranging from 293.0-2344.0 and 1172.0-4688.0, respectively. Methanol/DCM extracts showed significant to moderate activity against the susceptible TB strain and moderate to weak activity against the MDR-TB strain with MIC (μg/mL) ranging from 98.0-586.0 and 293.0-781.0, respectively. One mortality was recorded from the A. coriaria treated group following the acute toxicity tests, but the LD50 of all the extracts was estimated to be above 2000 mg/kg. Histopathological analyses did not show any significant lesions in the examined organs except those from the A. coriaria treated group.
CONCLUSION: Phytochemical screening of the extracts revealed the presence of alkaloids, tannins, saponins, flavonoids, steroids, terpenoids, resins, cardiac glycosides, phenolic compounds, and coumarins. All the methanol/DCM extracts of the plant species studied have promising antimycobacterial activity. The selected plant extracts studied exhibited low acute toxicity levels except for A. coriaria and could be safe for formulations into herbal products.

DOI: 10.1186/s41182-022-00406-7
PMID: 35177126

59. **Detection of Mycobacterium tuberculosis and rifampicin resistance by Xpert® MTB/RIF assay among presumptive tuberculosis cases at Jimma University Medical Center, Southwest Ethiopia.**

PLoS One. 2022 Jan 27;17(1):e0262929. doi: 10.1371/journal.pone.0262929. eCollection 2022.

Admassu W(1), Ayelign B(2), Abebe G(3)(4), Tadesse M(3)(4).

BACKGROUND: Rapid diagnosis of tuberculosis (TB) and detection of drug resistance are very important for timely and appropriate management of patients. Xpert MTB/RIF assay is approved for use in TB and rifampicin-resistance diagnosis. However, data are limited on the impact of Xpert MTB/RIF assay under routine clinical settings with a heterogeneous group of patients and sample types in Ethiopia.
METHODS: A retrospective study was carried out in 2220 presumptive TB cases at Jimma University Medical Center. Data were gathered from the registration logbook using formatted data extraction tools and double entered to epidata version 3.1 and further transported to SPSS version 20 for analysis. Associations were determined using the Chi-square test and P-value <0.05 was

considered statistically significant.
RESULTS: Of 2220 cases enrolled, 1665 (75%) were adults and the remaining 555 (25%) were children aged less than 14 years. The majority, 1964 (88.46%), had pulmonary manifestation and 256 (11.54%) had extrapulmonary involvements. The overall, frequency of Mycobacterium tuberculosis (MTB) was 9.3% (206/2220), among this 10.27% (171/1665) and 6.3% (35/555) were adults and children, respectively. M. tuberculosis was detected from 171 (8.75%) of pulmonary patients and 35 (13.28%) of extrapulmonary manifested patients. Out of 206 M. tuberculosis positive cases, 7(3.4%) were rifampicin-resistant: four from pulmonary tuberculosis (PTB) patients and three from EPTB patients. In the Chi-square test, the age group of 15-24 years, previous history of TB, pus/lymph node sample, and being HIV positive were significantly associated with TB positivity by Xpert MTB/RIF (P-value <0.001).
CONCLUSION: These data suggest that the overall frequency of M. tuberculosis and rifampicin resistance was found to be relatively low compared to the previous reports in Ethiopia. Nevertheless, better diagnostic tools and approaches are still vital to halt the burden of TB and drug-resistant TB in the country.

DOI: 10.1371/journal.pone.0262929
PMCID: PMC8794184
PMID: 35085337

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

Proteins. 2022 Feb;90(2):566-578. doi: 10.1002/prot.26253. Epub 2021 Oct 19.

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

Currently, multidrug-resistant tuberculosis (MDR-TB) is a public health crisis and a major health security threat globally. In Mycobacterium tuberculosis (Mtb), major facilitator superfamily (MFS) is the largest group of secondary active transporters. Along with the transport of their natural substrates, MFS proteins were involved in a drug efflux mechanism that ultimately lead to resistance against available anti-TB drugs in Mtb. In the present study, the three-dimensional structure model of an MFS protein, Rv1634, a probable multidrug transporter from Mtb, was generated using homology modeling. The protein structure model was found in inward-open conformation having 14 transmembrane helices. In addition, a central transport channel was deduced across the protein, and a single binding pocket was identified halfway through the central cavity by structural alignment with the homologous protein structures. Further, Rv1634 protein was studied based on the differential

structural behavior of apo and ligand-bound forms. All the protein systems were inserted into a phospholipid bilayer to characterize the conformational dynamics of the protein using molecular dynamics (MD) simulations. Detailed analysis of the MD trajectories showed the diverse substrate specificity of the binding pocket for the antibiotics that caused differential movement in the ciprofloxacin and norfloxacin, to which Mtb strains have now become resistant. The expulsion of the drugs outside the bacterial cell occurs through the alternating-access mechanism of N and C-terminal domains, which is intriguing and essential to the understanding the drug resistance mechanism in pathogenic bacteria.

DOI: 10.1002/prot.26253
PMID: 34601761

61. **D-Cycloserine-Induced Seizure Activity in the Emergency Department: A Case Report.**

J Pharm Pract. 2022 Feb 3:8971900221074955. doi: 10.1177/08971900221074955. Online ahead of print.

Kuhrau S(1), Boykin T(2), Rech MA(1)(2).

D-cycloserine (DCS) is an anti-tuberculosis medication that has been utilized for years for drug-resistant tuberculosis. DCS works via a centrally acting mechanism which can cause neurotoxic adverse effects which has limited its use. This centrally acting mechanism also allows for DCS to be utilized for various neuropsychiatric purposes. Our patient was on high-dose DCS for autism spectrum disorder and presented to the emergency department (ED) with a seizure. The seizure episode was managed with both anti-epileptics and pyridoxine. With increasing novel use of this older medication, it is imperative for ED clinicians to be aware of the different management strategies that may be required when a patient presents with a neurotoxic effect, specifically seizures, secondary to DCS.

DOI: 10.1177/08971900221074955
PMID: 35109718

62. **Has the Time Come for Systematic Therapeutic Drug Monitoring of First-Line and WHO Group A Antituberculosis Drugs?**

Ther Drug Monit. 2022 Feb 1;44(1):133-137. doi: 10.1097/FTD.0000000000000948.

Lemaitre F(1)(2).

Tuberculosis (TB) is a major global health issue, with approximately 10 million people being infected each year, and is the leading cause of mortality from infectious disease, with 1.5 million deaths a year. Optimal TB treatment requires a combination of drugs for an adequate treatment duration owing to persistent organisms, hardly accessible infection sites, and a high risk of resistance selection. Long-term therapy increases the risk of patients' loss of adherence, adverse drug reactions, and drug-drug interactions, potentially leading to treatment failure. The high interpatient variability of TB drug exposure is another point eliciting interest in therapeutic drug monitoring (TDM) to optimize treatment. Studies reporting clinically relevant exposure thresholds, which might be proposed as targets toward treatment personalization, are discussed. Practical TDM strategies have also been reported to circumvent issues related to delayed drug absorption and the need for multiple samples when evaluating the area under the curve of drug concentrations. The need for treatment individualization is further emphasized because of the development of multidrug-resistant TB or extensively drug-resistant TB. Finally, the willingness to shorten the treatment duration while maintaining success is also a driver for ensuring adequate exposure to TB drugs with TDM. The aim of the present review was to underline the role of TDM in drug-susceptible TB and World Health Organization group A TB drugs.

DOI: 10.1097/FTD.0000000000000948
PMID: 34857693

63. **Prevalence of toxoplasmosis in patients infected with tuberculosis; a sero-molecular case-control study in northwest Iran.**

Comp Immunol Microbiol Infect Dis. 2022 Feb;81:101720. doi: 10.1016/j.cimid.2021.101720. Epub 2021 Nov 18.

Parsaei M(1), Spotin A(2), Matini M(1), Mahjub H(3), Aghazadeh M(4), Ghahremani G(5), Taherkhani H(6).

In this study, we investigated the possible association between TB and Toxoplasma gondii infection. One hundred confirmed TB individuals living in northwest Iran were classified into three subgroups; newly diagnosed patients (NTB), old diagnosed patients (OTB) and multidrug resistance patients (MDR-TB).

One hundred healthy subjects in the same age and sex distribution were ethnically matched. Sera samples were screened for anti-Toxoplasma antibodies. Nested-PCR was performed by targeting the B1 and GRA6 genes. The frequency of Toxoplasma infection based on IgG titer was 71.1% in the OTB subgroup and 33% in the control group, indicating significant association between Toxoplasma seropositivity and OTB (P = 0.001). According to phylogenetic network, the type I strain of Toxoplasma was identified in the OTB subgroup (10.1%). We concluded that patients with OTB subgroup are at high risk for acquisition of Toxoplasma infection which could reactivate the latent toxoplasmosis.

DOI: 10.1016/j.cimid.2021.101720
PMID: 34990934 [Indexed for MEDLINE]

64. **Feasibility of a "Salvage Regimen" Using Home-based Intravenous Meropenem Therapy With a Delamanid/Bedaquilline Containing Regimen in the Management of MDR/XDR Pediatric Tuberculosis.**

Pediatr Infect Dis J. 2022 Feb 10. doi: 10.1097/INF.0000000000003486. Online ahead of print.

Shah I(1), Antony S, Jaiswal A, Bodhanwala M, Shah D, Tipre P, Salve J, Parmar M, Sachdeva KS.

INTRODUCTION: The prevalence of multidrug resistant (MDR) tuberculosis (TB) with additional resistance to fluoroquinolones or second-line injectables (MDRFQ/SLI)/extensively drug-resistant TB (XDR-TB) in children is high in Mumbai. There are limited therapeutic options available in management of such children. Carbapenems, although approved for this indication, requires 2 to 3 daily injections, which are cumbersome. Bedaquilline (Bdq) and Delamanid (Dlm), the new antitubercular drugs still remain inaccessible to this subset of patients caused by conditional approvals. Hence, newer strategies to combat MDRFQ/SLI/XDR-TB needs to be explored.
OBJECTIVES: To study feasibility and interim outcomes of a "salvage regimen" using home-based carbapenem therapy through peripherally inserted central catheter as part of a longer (18-20 months) optimized background regimen including Dlm or Bdq or both in pediatric MDRFQ/SLI/XDR-TB patients who failed a standard MDR-TB regimen under the National Tuberculosis Elimination Programme in Mumbai, India.
DESIGN AND METHODS: Retrospective descriptive analysis study. National Tuberculosis Elimination Programme medical records of all MDRFQ/SLI/XDR-TB patients enrolled at the pediatric TB clinic at BJ Wadia Hospital for Children,

Mumbai who were initiated on such "salvage regimen" during the period between April 2018 and December 2020 were retrospectively studied. Treatment outcomes and adverse events were described.
RESULTS: Of the 15 patients enrolled, mean age of the patient population was 12.53 ± 2.47 years and the female:male ratio was 13:2. Seven patients had XDR-TB while 8 patients had MDRFQ/SLI. Most common adverse event noted was dyselectrolytemia (3 patients). Catheter-related complications were reported in 5 patients and included catheter blockage, leak, and thrombosis. Sputum culture conversion was reported in all of the patients. One child mortality was reported and 2 patients were lost to follow up during study period.
CONCLUSIONS: Home-based meropenem therapy using peripherally inserted central catheter is feasible with few adverse effects. This can be a promising strategy in the management of MDRFQ/SLI/XDR-TB when an effective oral regimen cannot be otherwise constituted and needs to be explored further.

DOI: 10.1097/INF.0000000000003486
PMID: 35153288

65. **Characteristics of tuberculosis-related deaths and risk factors: a retrospective cohort study in Samsun province of Turkey.**

Postgrad Med. 2022 Jan 26:1-7. doi: 10.1080/00325481.2022.2029106. Online ahead of print.

Oruç MA(1), Ozdemir S(2), Oztomurcuk D(2).

OBJECTIVES: Tuberculosis (TB) remains one of the top ten leading causes of death worldwide despite effective therapy. The present study aims to examine the characteristics of TB-related deaths in Samsun Province and to determine the risk factors.
METHODS: In this retrospective registry-based cohort study, the medical records of patients registered with Samsun Tuberculosis Control Dispensary between 1 January 2018 and 31 December 2019 were retrospectively reviewed. The Cox proportional-hazards model was used to determine the factors associated with the risk of death in patients with TB.
RESULTS: The treatment outcomes of a total of 382 patients were reviewed. It was found that the treatment was successful in 346 patients (90.6%), and 31 patients (8.1%) died before or during TB therapy. The median survival time of patients who died during the therapy was 1.86 months (95% CI = 0.07-5.17 months), and more than 50% (13/25) of the deaths occurred in the first two months of the treatment. Age above 70 years (HR 15.06 (3.33-67.95)), male gender (HR 2.74

(1.02-7.33)), pulmonary TB (HR 2.92 (1.002-8.52)), multidrug-resistant (MDR) tuberculosis (HR 1.69 (1.22-12.75)), and a delay in the treatment of more than ten days (HR 2.71 (1.22-6.04)) were identified as risk factors associated with mortality in TB patients ($p < 0.05$).
CONCLUSION: The majority of deaths in our cohort occurred within the first two months after starting the treatment. Advanced age, male sex, a new diagnosis of TB, pulmonary TB, MDR-TB, and a treatment delay of more than ten days after diagnosis increased the risk for mortality during antituberculosis treatment.

DOI: 10.1080/00325481.2022.2029106
PMID: 35048749

66. **Clinical guidelines for managing hearing loss as a complication of drug-resistant tuberculosis treatment: an evaluation of implementation fidelity in Kano, Nigeria.**

BMC Health Serv Res. 2022 Feb 3;22(1):142. doi: 10.1186/s12913-022-07536-y.

Muhammad SI(1)(2), Eboreime EA(3), Ogbonna VI(4), Zubairu I(5), Ibisomi L(6)(7).

BACKGROUND: Nigeria has a high burden of Tuberculosis (TB) including Drug-resistant Tuberculosis (DR-TB) and hearing loss. Despite several efforts directed toward its control, many patients fail to respond to treatment, having developed DR-TB. Lack of adherence to the DR-TB guidelines/improper implementation of the guideline has been identified as one of the factors impeding on effective treatment. This study sought to measure the implementation fidelity of health workers to management guidelines for hearing loss resulting from DR-TB treatment and to identify its determinants.
METHOD: A questionnaire-based cross-sectional study was conducted at the Infectious Disease Hospital, Kano. Implementation fidelity of the Programmatic Management guidelines for the treatment of Drug-resistant Tuberculosis was measured under the four domains of content, coverage, duration and frequency. The determinants examined are intervention complexity, facilitation strategies, quality of delivery and participant responsiveness as proposed by the Carroll et al. framework. Other determinants used are age, sex, professional cadre and work experience of healthcare providers.
RESULTS: The Implementation fidelity score ranged from 40 to 64% with a mean of 47.6%. Quality of delivery, intervention complexity, participants' responsiveness, and being a medical doctor exerted a positive effect on implementation fidelity while facilitation strategy, age and work experience exerted a negative effect on implementation fidelity.
CONCLUSION: The implementation fidelity of management guidelines for hearing loss resulting from DR-TB treatment was low. Implementation fidelity should be

assessed early and at intervals in the course of implementing the Programmatic Management of Drug-resistant Tuberculosis guideline and indeed, in the implementation of any intervention.

DOI: 10.1186/s12913-022-07536-y
PMCID: PMC8812187
PMID: 35115002 [Indexed for MEDLINE]

67. **Monitoring prolongation of QT interval in patients with multidrug-resistant tuberculosis and non-tuberculous mycobacterium using mobile health device AliveCor.**

J Clin Tuberc Other Mycobact Dis. 2021 Dec 18;26:100293. doi: 10.1016/j.jctube.2021.100293. eCollection 2022 Feb.

Puranik S(1), Harlow C(2), Martin L(2), Coleman M(2), Russell G(2), Park M(3), Min Kon O(4).

Multidrug resistant tuberculosis and non-tuberculous mycobacterium infections present challenges due to complex treatment regimens. Extended treatment regimes expose patients to higher risks of toxic side-effects. A high drug toxicity profile necessitates closer monitoring. One of the more challenging issues is QTc prolongation with non-injectable regimens. This study investigates the portable AliveCor device to record and measure the QTc on a 6-lead ECG. An automated QTc readout from 12-Lead ECG for each patient (n = 13) and mean QTc value calculated from each patients' respective AliveCor tracing were compared. The general trend suggests AliveCor underestimates QTc - 92% cases calculated the AliveCor QTc as lower than their corresponding 12-Lead QTc readout. The use of AliveCor could potentially be translated into current clinical practice with caution of percentage variation either side. This could facilitate the use of AliveCor as a promising and convenient screening tool before further evaluation by a 12-Lead ECG is required.

DOI: 10.1016/j.jctube.2021.100293
PMCID: PMC8802120
PMID: 35146132

68. **Pharmacogenetics of Between-Individual Variability in Plasma Clearance of**

Bedaquiline and Clofazimine in South Africa.

J Infect Dis. 2022 Jan 29:jiac024. doi: 10.1093/infdis/jiac024. Online ahead of print.

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

OBJECTIVE: Plasma bedaquiline clearance is reportedly more rapid with African ancestry. We examined whether genetic polymorphisms explained between-individual variability in plasma clearance of bedaquiline, its M2 metabolite, and clofazimine in a cohort of patients treated for drug-resistant tuberculosis in South Africa.
METHODS: Plasma clearance was estimated with non-linear mixed-effects modelling. Associations between pharmacogenetic polymorphisms, genome-wide polymorphisms, and variability in clearance were examined using linear regression models.
RESULTS: Of 195 cohort participants, 140 were evaluable for genetic associations. Among 21 polymorphisms selected based on prior genome-wide significant associations with any drug, rs776746 (CYP3A5*3) was associated with slower clearance of bedaquiline (p = 0.0017) but not M2 (p = 0.25). CYP3A5*3 heterozygosity and homozygosity were associated with 15% and 30% slower bedaquiline clearance, respectively. The lowest P-value for clofazimine clearance was VKORC1 rs9923231 (p = 0.13). In genome-wide analyses, the lowest P-values for clearance of bedaquiline and clofazimine were RFX4 rs76345012 (p = 6.4x10 -7) and CNTN5 rs75285763 (p = 2.9x10 -8), respectively.
CONCLUSIONS: Among South Africans treated for drug-resistant tuberculosis, CYP3A5*3 was associated with slower bedaquiline clearance. Different CYP3A5*3 frequencies among populations may help explain the more rapid bedaquiline clearance reported in Africans. Associations with RFX4 and CNTN5 are likely by chance alone.

DOI: 10.1093/infdis/jiac024
PMID: 35091749

69. **The Medicinal Chemistry of Chalcones as Anti-Mycobacterium tuberculosis Agents.**

Mini Rev Med Chem. 2022 Feb 14. doi: 10.2174/1389557522666220214093606. Online ahead of print.

Rodríguez-Silva CN(1), Prokopczyk IM(2), Dos Santos JL(3).

Tuberculosis (TB), a highly fatal infectious disease, is caused by Mycobacterium tuberculosis (Mtb) that has inflicted mankind for several centuries. In 2019, the staggering number of new cases reached 10 million resulting in 1.2 million deaths. The emergence of multidrug-resistance-Mycobacterium tuberculosis (MDR-TB) and extensively drug-resistant-Mycobacterium tuberculosis (XDR-TB) is a global concern that requires the search for novel, effective, and safer short-term therapies. Nowadays, among the few alternatives available to treat resistant-Mtb strains, the majority have limitations, which include drug-drug interactions, long-term treatment, and chronic induced toxicities. Therefore, it is mandatory to develop new anti-Mtb agents to achieve health policy goals to mitigate the disease by 2035. Among the several bioactive anti-Mtb compounds, chalcones have been described as the privileged scaffold useful for drug design. Overall, this review explores and analyzes 37 chalcones that exhibited anti-Mtb activity described in the literature up to April 2021 with minimum inhibitory concentration (MIC90) values inferior to 20 μM and selective index superior to 10. In addition, the correlation of some properties for most active compounds was evaluated, and the main targets for these compounds were discussed.

DOI: 10.2174/1389557522666220214093606
PMID: 35156577

70. **Seizures and sideroblastic anaemia in a patient with multidrug-resistant tuberculosis.**

Lancet. 2022 Jan 22;399(10322):393. doi: 10.1016/S0140-6736(22)00013-7.

Vigneshwaran J(1), Kumar MS(2), Raghavan V(3), Sundari S(3).

DOI: 10.1016/S0140-6736(22)00013-7
PMID: 35065787 [Indexed for MEDLINE]

71. **Minimizing nephrotoxicity during multidrug-resistant tuberculosis treatment by the stepwise de-escalation of second-line injectables dosing intervals.**

Clin Microbiol Infect. 2022 Feb 3:S1198-743X(22)00047-7. doi: 10.1016/j.cmi.2022.01.023. Online ahead of print.

Lin HC(1), Yu MC(2), Putri DU(1), Tsai YS(3), Chen JH(4), Lee CH(5).

DOI: 10.1016/j.cmi.2022.01.023
PMID: 35124260

72. **Detection of isoniazid, fluoroquinolone, ethionamide, amikacin, kanamycin, and capreomycin resistance by the Xpert MTB/XDR assay: a cross-sectional multicentre diagnostic accuracy study.**

Lancet Infect Dis. 2022 Feb;22(2):242-249. doi: 10.1016/S1473-3099(21)00452-7. Epub 2021 Oct 7.

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

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

detection) was 2·96%.
INTERPRETATION: The Xpert MTB/XDR assay showed high diagnostic accuracy and met WHO's minimum target product profile criteria for a next-generation drug susceptibility test. The assay has the potential to diagnose drug-resistant tuberculosis rapidly and accurately and enable optimum treatment.
FUNDING: German Federal Ministry of Education and Research through KfW, Dutch Ministry of Foreign Affairs, and Australian Department of Foreign Affairs and Trade.

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

73. **Unraveling the possible inhibitors for Chorismate synthase to combat tuberculosis using in silico approach.**

J Biomol Struct Dyn. 2022 Feb 15:1-8. doi: 10.1080/07391102.2022.2039298. Online ahead of print.

Hanif M(1), Khan S(2), Farooq U(2), Nouroz F(1), Sarwar R(2).

Tuberculosis antibiotic resistance is a huge concern to the global population. The goal of this study was to find new and effective compounds to treat multidrug-resistant tuberculosis by targeting Chorismate synthase (CS), a crucial enzyme for Mycobacterium tuberculosis survival (MbT). The potential of a library of compounds as selective anti - tuberculosis drugs was investigated. Docking was first conducted using MoE to determine the effectiveness of the compounds. Molecular docking studies followed by MD simulation studies (total of 500 ns) in combination with free energy calculations grade the ligands in terms of their binding affinities. In the ligand bound state of the CS, MD simulations revealed a change from stretched to bended motional shift in loop L19. The RMSF analysis also revealed this flexibility, which was confirmed by visual inspection of L19 at various time intervals during the experiment. It appears that ZF1(-25.43Kcal/mol) and ZF2 (-22.04Kcal/mol) form hbonds and have a high binding energy in the active region of protein. Residues wise distribution of binding energy reveals that Arg144, Trp4, Thr6, and L19 amino acid residues are engaged in binding of CS with inhibitors. In summary, the findings suggest that compounds ZF1 and ZF2 may be more effective and selective anti-TB agents than currently available drugs. Also the role of L19, mediated by αH9 and αH5 in the retention of ligand inside the active pocket, through the formation of lid was also revealed. This knowledge will aid in the discovery of drugs that are potent CS inhibitors. More experimental research and a better understanding of the

structure-activity relationship could aid in the development of possible candidates with better CS inhibition.Communicated by Ramaswamy H. Sarma.

DOI: 10.1080/07391102.2022.2039298
PMID: 35168481

74. **Patterns of genomic interrelatedness of publicly available samples in the TB portals database.**

Tuberculosis (Edinb). 2022 Jan 24;133:102171. doi: 10.1016/j.tube.2022.102171. Online ahead of print.

Wollenberg KR(1), Jeffrey BM(2), Harris MA(3), Gabrielian A(4), Hurt DE(5), Rosenthal A(6).

The TB Portals program is an international collaboration for the collection and dissemination of tuberculosis data from patient cases focused on drug resistance. The central database is a patient-oriented resource containing both patient and pathogen clinical and genomic information. Herein we provide a summary of the pathogen genomic data available through the TB Portals and show one potential application by examining patterns of genomic pairwise distances. Distributions of pairwise distances highlight overall patterns of genome variability within and between Mycobacterium tuberculosis phylogenomic lineages. Closely related isolates (based on whole-genome pairwise distances and time between sample collection dates) from different countries were identified as potential evidence of international transmission of drug-resistant tuberculosis. These high-level views of genomic relatedness provide information that can stimulate hypotheses for further and more detailed research.

DOI: 10.1016/j.tube.2022.102171
PMID: 35101846

75. **1H-1,2,3-triazole embedded Isatin-Benzaldehyde-bis(heteronuclearhydrazones): design, synthesis, antimycobacterial, and cytotoxic evaluation.**

Chem Biol Drug Des. 2022 Feb;99(2):301-307. doi: 10.1111/cbdd.13984. Epub 2021 Nov 25.

Sharma B(1), Kumar S(1), Preeti(1), Johansen MD(2)(3), Kremer L(2)(4), Kumar V(1).

Rapid growth of global drug-resistant tuberculosis and urgent requirement for short treatment regimens is stimulating the need for discovery of new TB drugs. In this work, we report the design, synthesis and in vitro antimycobacterial evaluation of a library of isatin-derived bis(heteronuclear hydrazones). Evaluation results revealed that the inclusion of isoniazid core into 1H-1,2,3-triazole tethered isatin-benzaldehydes improved the antimycobacterial activity on tuberculosis mc2 6230 strain and significantly reduced the cytotoxicity against Vero cells. However, the introduction of semicarbazones/thiosemicarbazones or pyrazine-2-carbohydrazide produced the opposite effects. The compounds with isoniazid and polar-donating groups at the C-5 position of isatin emerged as the most promising conjugates with MIC99 = 0.36 μg/ml. The most active compounds were non-cytotoxic to Vero cells (IC50 >100 μg/ml) with selectivity indices >277.

DOI: 10.1111/cbdd.13984
PMID: 34786862

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

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

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

Tuberculosis (TB) is the leading infectious disease caused by Mycobacterium tuberculosis (Mtb). Clarithromycin (CTY), an analog of erythromycin (ERY), is more potent against multidrug-resistance (MDR) TB. ERY and CTY were previously reported to bind to the nascent polypeptide exit tunnel (NPET) near peptidyl transferase center (PTC), but the only available CTY structure in complex with D. radiodurans (Dra) ribosome could be misinterpreted due to resolution limitation. To date, the mechanism of specificity and efficacy of CTY for Mtb remains elusive since the Mtb ribosome-CTY complex structure is still unknown. Here, we employed new sample preparation methods and solved the Mtb ribosome-CTY complex structure at 3.3Å with cryo-EM technique, where the crucial gate site A2062 (E. coli numbering) is located at the CTY binding site within NPET. Two alternative conformations of A2062, a novel syn-conformation as well as a swayed conformation bound with water molecule at interface, may play a role in coordinating the binding of specific drug molecules. The previously overlooked

C-H hydrogen bond (H-bond) and π interaction may collectively contribute to the enhanced binding affinity. Together, our structure data provide a structural basis for the dynamic binding as well as the specificity of CTY and explain of how a single methyl group in CTY improves its potency, which provides new evidence to reveal previously unclear mechanism of translational modulation for future drug design and anti-TB therapy. Furthermore, our sample preparation method may facilitate drug discovery based on the complexes with low water solubility drugs by cryo-EM technique.

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

77. **Experimental confirmation that an uncommon rrs gene mutation (g878a) of Mycobacterium tuberculosis confers resistance to streptomycin.**

Antimicrob Agents Chemother. 2022 Jan 24:AAC0191521. doi: 10.1128/AAC.01915-21. Online ahead of print.

Domenech P(1)(2), Mouhoub E(1)(2)(3), Reed MB(1)(2)(3)(4).

The effective treatment of patients diagnosed with drug resistant tuberculosis is highly dependent upon the ability to rapidly and accurately determine the antibiotic susceptibility profile of the Mycobacterium tuberculosis isolate(s) involved. Thus, as more clinical microbiology laboratories advance towards the use of DNA sequence-based diagnostics, it is imperative that their predictive functions extend beyond the well-known resistance mutations, in order to also encompass as many of the lower-frequency mutations as possible. However, in most cases, the fundamental experimental proof that links these uncommon mutations with phenotypic resistance is lacking. One such example is the g878a polymorphism within the rrs 16s rRNA gene. We, and others, have identified this mutation within a small number of drug-resistant isolates, although a consensus regarding exactly which aminoglycoside antibiotic(s) it confers resistance toward has not previously been reached. Here we have employed oligo-mediated recombineering to introduce the g878a polymorphism into the rrs gene of M. bovis BCG - a close relative of M. tuberculosis - and demonstrate that it confers low-level resistance to streptomycin alone. It does not confer cross-resistance towards amikacin, capreomycin, nor kanamycin. We also demonstrate that the rrsg878a mutation exerts a substantial fitness defect in vitro, that may at least in part explain why clinical isolates bearing this mutation appear to be quite rare. Overall, this study provides clarity to the phenotype attributable to the rrsg878a mutation and is relevant to the future implementation of genomics-based diagnostics, as well as the clinical management of patients where

this particular polymorphism is encountered.

DOI: 10.1128/AAC.01915-21
PMID: 35072512

78. **The Role of GeneXpert MTB/RIF in Reducing Treatment Delay Among Multidrug Resistance Tuberculosis Patients: A Propensity Score Matched Analysis.**

Infect Drug Resist. 2022 Jan 27;15:285-294. doi: 10.2147/IDR.S345619.
eCollection 2022.

Tamirat KS(1), Kebede FB(2), Baraki AG(1), Akalu TY(1).

BACKGROUND: GeneXpert MTB/RIF testing is a rapid molecular diagnostic test that is performed with an automated cartilage-based machine that makes treatment initiation prompt. This study aimed at evaluating the impact of GeneXpert in the reduction of treatment delay among multidrug-resistant tuberculosis (MDR-TB) patients in Amhara regional state of Ethiopia.
METHODS: A facility-based retrospective follow-up study was conducted from January to February 2019, and a total of 465 MDR-TB patients were included in the study. Socio-demographic, clinical, and treatment-related characteristics were collected from patient's chart retrospectively using data abstraction sheets. Binary logistic regression model was fitted to identify factors associated with treatment delay; adjusted odds ratio (AOR) with a 95% confidence interval (CI) was computed to assess the strength of association. A propensity score-matched (PSM) analysis was used to assess the impact of the GeneXpert MTB/RIF test on treatment delay through calculation of average treatment effect (ATE).
RESULTS: The majority, 92.4%, of patients had the pulmonary form of TB, and 46.7% of patients were diagnosed by GeneXpert MTB/RIF. The presence of cavitation (AOR = 0.62, 95% CI: 0.39 0.96), extrapulmonary form of TB (AOR = 0.34, 95% CI: 0.14 0.81), and GeneXpert (AOR = 0.15, 95% CI: 0.10 0.24) were factors associated with treatment delay. The average treatment effect (ATE) of PSM analysis showed that GeneXpert MTB/RIF has significantly reduced treatment delay by 41% compared to matched control groups.
CONCLUSION: This study revealed that GeneXpert test has a strong association with the reduced treatment delays among MDR-TB patients. This underscores that rapid molecular tests could help improve the health system and lead to prompt initiation of MDR-TB treatment. Therefore, expansion and decentralization of GeneXpert tests to peripheral health facilities are highly recommended. In turn, the case detection and control of the disease will be hastened.

DOI: 10.2147/IDR.S345619
PMCID: PMC8803608
PMID: 35115796

79. **Fluoroquinolone preventive therapy for children exposed to MDR-TB.**

Int J Tuberc Lung Dis. 2022 Feb 1;26(2):171-173. doi: 10.5588/ijtld.21.0443.

Gureva T(1), Turkova A(2), Yablokova E(1), Smirnova P(3), Sveshnikova O(3), Zolotaya O(3), Nikishova E(1), Heldal E(4), Hinderaker S(5), Seddon JA(6), Mariandyshev A(7).

DOI: 10.5588/ijtld.21.0443
PMCID: PMC8802561
PMID: 35086631