Pub Med Open Access

1. Clofazimine: A journey of a drug.

Biomed Pharmacother. 2023 Nov;167:115539. doi: 10.1016/j.biopha.2023.115539. Epub 2023 Sep 22.

Xu J(1), Koval A(1), Katanaev VL(2).

Among different strategies to develop novel therapies, drug repositioning (aka repurposing) aims at identifying new uses of an already approved or investigational drug. This approach has the advantages of availability of the extensive pre-existing knowledge of the drug's safety, pharmacology and toxicology, manufacturing and formulation. It provides advantages to the risk-versus-rewards trade-off as compared to the costly and time-consuming de novo drug discovery process. Clofazimine, a red-colored synthetic derivative of riminophenazines initially isolated from lichens, was first synthesized in the 1950 s, and passed through several phases of repositioning in its history as a drug. Being initially developed as an anti-tuberculosis treatment, it was repurposed for the treatment of leprosy, prior to re-repositioning for the treatment of multidrug-resistant tuberculosis and other infections. Since 1990 s, reports on the anticancer properties of clofazimine, both in vitro and in vivo, started to appear. Among the diverse mechanisms of action proposed, the activity of clofazimine as a specific inhibitor of the oncogenic Wnt signaling pathway has recently emerged as the promising targeting mechanism of the drug against breast, colon, liver, and other forms of cancer. Seventy years after the initial discovery, clofazimine's journey as a drug finding new applications continues, serving as a colorful illustration of drug repurposing in modern pharmacology.

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PMID: 37742606 [Indexed for MEDLINE]

Conflict of interest statement: Declaration of Competing Interest The authors declare that they have no conflict of interests.

2. Advanced drug delivery and therapeutic strategies for tuberculosis treatment.

J Nanobiotechnology. 2023 Nov 9;21(1):414. doi: 10.1186/s12951-023-02156-y.

Nair A(1), Greeny A(2), Nandan A(2), Sah RK(2), Jose A(3), Dyawanapelly S(4), Junnuthula V(5), K V A(6), Sadanandan P(7).

Tuberculosis (TB) remains a significant global health challenge, necessitating innovative approaches for effective treatment. Conventional TB therapy encounters several limitations, including extended treatment duration, drug resistance, patient noncompliance, poor bioavailability, and suboptimal targeting. Advanced drug delivery strategies have emerged as a promising approach to address these challenges. They have the potential to enhance therapeutic outcomes and improve TB patient compliance by providing benefits such as multiple drug encapsulation, sustained release, targeted delivery, reduced dosing frequency, and minimal side effects. This review examines the current landscape of drug delivery strategies for effective TB management, specifically highlighting lipid nanoparticles, polymer nanoparticles, inorganic nanoparticles, emulsion-based systems, carbon nanotubes, graphene, and hydrogels as promising approaches. Furthermore, emerging therapeutic strategies like targeted therapy, long-acting therapeutics, extrapulmonary therapy, phototherapy, and immunotherapy are emphasized. The review also discusses the future trajectory and challenges of developing drug delivery systems for TB. In conclusion, nanomedicine has made substantial progress in addressing the challenges posed by conventional TB drugs. Moreover, by harnessing the unique targeting abilities, extended duration of action, and specificity of advanced therapeutics, innovative solutions are offered that have the potential to revolutionize TB therapy, thereby enhancing treatment outcomes and patient compliance.

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PMCID: PMC10634178
PMID: 37946240 [Indexed for MEDLINE]

Conflict of interest statement: The authors declare no competing interests, financial or otherwise.

3. Call for special attention to the caregiver burden of patients with drug-resistant tuberculosis in low- and middle-income countries.

Biosci Trends. 2023 Nov 18;17(5):405-408. doi: 10.5582/bst.2023.01243. Epub 2023 Oct 14.

Wu S(1), Zhang H(1), Wang Y(1), Wang J(1), Zhang P(1), Asakawa T(2), Lin Y(1).

The tuberculosis (TB)-related caregiver burden (CB), and particularly the multidrug and extensively drug-resistant tuberculosis (M/XDR-TB)-related CB, is not rare in caregivers caring for TB patients, especially when a family member is the caregiver. However, the existing studies on this topic are insufficient. This study briefly summarized the risk factors for the imposition of a TB-related CB and reasons why caregivers for patients with M/XDR-TB are more susceptible to a CB. We propose that special measures should be implemented to alleviate the TB-related CB based on our clinical experience and insights from China. This may improve the situation of caregivers for TB patients and ultimately improve the quality of life of TB patients.

DOI: 10.5582/bst.2023.01243
PMID: 37839889

4. Analysis of Drug-Resistant Tuberculosis in Children in Shenyang, China, 2017-2021.

Infect Drug Resist. 2023 Nov 1;16:6983-6998. doi: 10.2147/IDR.S428720. eCollection 2023.

Sun J(#)(1), Fan L(#)(2), Zhao Y(#)(3), Wu H(2), Li R(2), Tian Y(2), Cheng M(2), Ma X(1), Ma Y(1), Yang X(1), Shen A(4), Yu Y(1), Chen Y(2).

OBJECTIVE: Drug-resistant tuberculosis (DR-TB) in children seriously threatens TB control. Information on the epidemiology and characteristics of DR-TB in children in China is limited. We studied data in Shenyang Tenth People's Hospital to understand the DR-TB epidemiology in children in Shenyang.
DESIGN OR METHODS: We retrospectively analyzed drug resistance testing data of pediatric TB patients between 2017 and 2021, and included 2976 clinically-diagnosed pediatric TB patients. We described the epidemiology of DR-TB and analyzed the trends of DR-TB incidence. The Kappa value was calculated to assess the agreement between MGIT 960 DST and Xpert MTB/RIF for detecting rifampicin resistance. Multivariate logistic regression was used to identify the risk factors for DR-TB in pediatric patients.
RESULTS: Of the 2976 TB patients, 1076 were confirmed by MGIT 960 culture and/or Xpert MTB/RIF. Among the 806 patients identified by MGIT 960 culture, 232 cases (28.78%) were DR-TB. Resistance to the six drugs was in the following order: streptomycin (21.09%), isoniazid (9.35%), rifampin (15.01%), levofloxacin (6.20%), ethambutol (4.22%), and amikacin (3.23%). Alarmingly, 12.90% were MDR-TB (104/806), including 28 (3.47%) pre-XDR-TB. Of the 1076 pediatric TB patients, 295 (27.4%) developed DR-TB to any one drug (including 69 rifampicin-resistant cases identified by Xpert MTB/RIF only). No difference was found in the incidence of pediatric DR-TB between 2017 and 2021. Among 376

patients who were positive for both methods, using the MGIT 960 DST results as the gold standard, Xpert MTB/RIF's sensitivity for detecting rifampicin resistance was 91.38% and its specificity was 94.65%.
CONCLUSION: Between 2017 and 2021, the DR-TB incidence in children remained unchanged in Shenyang. RR-TB, MDR-TB, and even Pre-XDR-TB require attention in children with drug-resistant TB. Xpert MTB/RIF helped to detect more rifampicin-resistant pediatric patients; thus Xpert MTB/RIF should be widely used as an important complementary tool to detect rifampicin-resistant TB in children.

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PMCID: PMC10625755
PMID: 37933293

Conflict of interest statement: The authors declare that there is no commercial/financial or other conflicts of interest involved.

5. Pediatric multi-drug-resistant tuberculosis in Germany - diagnostic and therapeutic challenges of an "orphan disease".

Eur J Pediatr. 2023 Nov;182(11):5167-5179. doi: 10.1007/s00431-023-05167-x. Epub 2023 Sep 14.

Schäfer HL(1), Barker M(2), Follmann P(3), Günther A(2), Hörning A(4), Kaiser-Labusch P(5), Kerzel S(6), Maier C(7), Roth S(6), Schmidt C(8), Schütz K(9), Stehling F(10), Struffert M(7), Timmesfeld N(11), Vöhringer P(12), Brinkmann F(7)(13).

Delay in diagnosing multidrug-resistant tuberculosis (MDR-pTB) in children prolongs time to effective treatment. Data on risk factors for pediatric MDR from low-incidence countries are scarce. Retrospective nationwide case-control study to analyze MDR-pTB cases in Germany between 2010 and 2020 in comparison to a drug-susceptible (DS)-pTB group. We included 52 MDR cases (24 tuberculosis (TB), 28 TB infection (TBI); mean age 7.3 years) and 56 DS cases (31 TB, 26 TBI; mean age 7.9 years). Groups were similar for sex, household size, and migration background. Compared to the DS group, more children with MDR were born in the Commonwealth of Independent States (CIS) (22% MDR-pTB vs. 13% DS-pTB, n.s.) and had more MDR index cases (94% MDR-pTB, 5% DS-pTB, $p < 0.001$). The interval between first healthcare contact and initiation of effective therapy was significantly longer in MDR-pTB (47 days) than in DS-pTB (11 days, $p < 0.001$), correlating with disease progression. Treatment for MDR-pTB was successful in

74%, but 22% experienced long-term adverse effects (e.g., hepatopathy, hearing loss).
CONCLUSIONS: Close contact to MDR cases or birth in MDR-TB-high-incidence countries are risk factors for MDR-pTB. Early identification of potential MDR index cases by contact investigation, and susceptibility testing in children from high-burden MDR-TB countries are essential for timely diagnosis and treatment, reducing the severity of disease and treatment side effects.
TRIAL REGISTRATION: Deutsches Register Klinischer Studien (https://www.drks.de/drks_web/navigate.do?navigationId=trial.HTML&TRIAL_ID=DRKS00023817), DRKS00023817, 2020-09-08.
WHAT IS KNOWN: •Management of children with MDR-TB remains challenging due to difficulties in diagnosing MDR-TB (lack of information on MDR index case, lack of microbiological confirmation in paucibacillary disease). •Choice of treatment regimen and monitoring of side effects.
WHAT IS NEW: •Children with an MDR-TB index or born in a MDR-TB-high-incidence country are at higher risk of developing MDR-TB in a low incidence country. •The time lag to initiate treatment in MDR-TB is longer than in DS-TB and MDR-TB treatment involves a higher risk of adverse effects in longer treatment regimens especially with injectables.

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PMCID: PMC10640426
PMID: 37707590 [Indexed for MEDLINE]

Conflict of interest statement: The authors have no relevant financial or non-financial interests to disclose.

6. The safety and efficacy of decortication for stage III drug-resistant tuberculous empyema.

Interdiscip Cardiovasc Thorac Surg. 2023 Nov 2;37(5):ivad166. doi: 10.1093/icvts/ivad166.

Yao L(1), Wang B(1), Chen X(1), Liu Q(1), Sheng J(1), Liu X(1), Dai X(1), Jiang Y(1).

OBJECTIVES: The goal of this study was to evaluate the safety and efficacy of decortication for stage III drug-resistant tuberculous empyema (TE).
METHODS: We analysed all patients with stage III TE who underwent decortication between March 2015 and October 2019 at Wuhan Pulmonary Hospital. The patients

were divided into 2 groups according to drug-susceptibility testing of bronchoscopy lavage fluid, pleural effusion and tissue specimens, including a drug-resistant group and a drug-sensitive group. We collected and compared the preoperative, perioperative and postoperative data from the 2 groups to evaluate the safety and efficacy of decortication for stage III drug-resistant TE.
RESULTS: In total, 135 cases met the inclusion criteria and were enrolled, including 30 cases in the drug-resistant group and 105 cases in the drug-sensitive group. No deaths were recorded for the entire study population. Compared to the drug-sensitive group, the drug-resistant group had longer operation times (259.8 ± 78.4 min vs 187.2 ± 56.0 min, P = 0.00), a larger volume of intraoperative blood loss [300 (200,400) ml vs 200 (130, 300) ml, P = 0.00] and a higher intraoperative transfusion rate (5/30, 16.7% vs 4/105, 3.8%, P = 0.04). The rate of complications was significantly higher in the drug-resistant group (23; 76.7%) than in the drug-sensitive group (53; 50.5%) (P = 0.01). Recurrence was not reported in any of the patients. Twenty-three (76.7%) patients in the drug-resistant group and 90 (85.7%) patients in the drug-sensitive group recovered to an "excellent" level, and 3 cases in each group recovered to a "poor" level; there was no significant difference between the 2 groups in surgical effects (P = 0.21).
CONCLUSIONS: Decortication is a safe, effective and feasible option for patients with stage III drug-resistant TE, although the operation is difficult and risky.

DOI: 10.1093/icvts/ivad166
PMCID: PMC10629925
PMID: 37812210

7. Costs of treating multidrug-resistant TB in California in 2022.

Int J Tuberc Lung Dis. 2023 Nov 1;27(11):864-866. doi: 10.5588/ijtld.23.0150.

Katrak S(1), Wang R(2), Barry P(1).

DOI: 10.5588/ijtld.23.0150
PMCID: PMC10599414
PMID: 37880888 [Indexed for MEDLINE]

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

8. Whole genome sequencing of drug resistance Mycobacterium tuberculosis from

extra-pulmonary sites.

Life Sci Alliance. 2023 Aug 17;6(11):e202302076. doi: 10.26508/lsa.202302076. Print 2023 Nov.

Shi T(1), Shou F(2), He Y(3), Zhou K(3), Gao W(3), Nie X(4), Han M(3), Liao C(5), Li T(6).

This study aimed to determinate characteristics of drug resistance Mycobacterium tuberculosis from patients with extra-pulmonary tuberculosis (EPTB). Patients were retrospectively studied from January 2020 to December 2021. All the isolates were cultured, tested drug susceptibility, and detected the gene mutation using whole genome sequencing. The correlations of whole genome sequencing, pattern of DR, patients' distribution, and transmission were analyzed. 111 DR-EPTB isolates included pre-XDR-TB (53.2%), MDR-TB (29.7%), and poly-DR-TB (12.6%). The resistant drugs were INH followed by RFP and SM. The genotypes of 111 strains were lineage 2 and lineage 4. KatG_p.Ser315Thr was main gene mutation for resistance to INH; rpsL_p.Lys43Arg for SM, rpoB_p.Ser450Leu for rifampicin, embB_p.Met306Val for ethambutol, gyrA_p.Asp94Gly for FQs, and pncA_p.Thr76Pro for PZA. The residence was a significant risk factor for cluster transmission by patients and phenotypic DR types of strains for lineage 2 transmission. In the local area of southwest China INH, rifampicin and SM were main drugs in patients with DR-EPTB. KatG_p.Ser315, rpoB_p.Ser450Leu, and rpsL_p.Lys43Arg were main gene mutations. Phenotypic DR types and residence were main risk of transmission.

DOI: 10.26508/lsa.202302076
PMCID: PMC10435967
PMID: 37591723 [Indexed for MEDLINE]

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

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

Lancet Microbe. 2023 Nov 3:S2666-5247(23)00172-6. doi: 10.1016/S2666-5247(23)00172-6. Online ahead of print.

Derendinger B(1), Dippenaar A(2), de Vos M(3), Huo S(4), Alberts R(1), Tadokera R(1), Limberis J(5), Sirgel F(1), Dolby T(6), Spies C(1), Reuter A(7), Folkerts M(8), Allender C(8), Lemmer D(8), Van Rie A(9), Gagneux S(10), Rigouts L(11), Te

Riele J(12), Dheda K(13), Engelthaler DM(8), Warren R(1), Metcalfe J(5), Cox H(14), Theron G(15).

BACKGROUND: Bedaquiline is a life-saving tuberculosis drug undergoing global scale-up. People at risk of weak tuberculosis drug regimens are a priority for novel drug access despite the potential source of Mycobacterium tuberculosis-resistant strains. We aimed to characterise bedaquiline resistance in individuals who had sustained culture positivity during bedaquiline-based treatment.
METHODS: We did a retrospective longitudinal cohort study of adults (aged ≥18 years) with culture-positive pulmonary tuberculosis who received at least 4 months of a bedaquiline-containing regimen from 12 drug-resistant tuberculosis treatment facilities in Cape Town, South Africa, between Jan 20, 2016, and Nov 20, 2017. Sputum was programmatically collected at baseline (ie, before bedaquiline initiation) and each month to monitor treatment response per the national algorithm. The last available isolate from the sputum collected at or after 4 months of bedaquiline was designated the follow-up isolate. Phenotypic drug susceptibility testing for bedaquiline was done on baseline and follow-up isolates in MGIT960 media (WHO-recommended critical concentration of 1 μg/mL). Targeted deep sequencing for Rv0678, atpE, and pepQ, as well as whole-genome sequencing were also done.
FINDINGS: In total, 40 (31%) of 129 patients from an estimated pool were eligible for this study. Overall, three (8%) of 38 patients assessable by phenotypic drug susceptibility testing for bedaquiline had primary resistance, 18 (47%) gained resistance (acquired or reinfection), and 17 (45%) were susceptible at both baseline and follow-up. Several Rv0678 and pepQ single-nucleotide polymorphisms and indels were associated with resistance. Although variants occurred in Rv0676c and Rv1979c, these variants were not associated with resistance. Targeted deep sequencing detected low-level variants undetected by whole-genome sequencing; however, none were in genes without variants already detected by whole-genome sequencing. Patients with baseline fluoroquinolone resistance, clofazimine exposure, and four or less effective drugs were more likely to have bedaquiline-resistant gain. Resistance gain was primarily due to acquisition; however, some reinfection by resistant strains occurred.
INTERPRETATION: Bedaquiline-resistance gain, for which we identified risk factors, was common in these programmatically treated patients with sustained culture positivity. Our study highlights risks associated with implementing life-saving new drugs and shows evidence of bedaquiline-resistance transmission. Routine drug susceptibility testing should urgently accompany scale-up of new drugs; however, rapid drug susceptibility testing for bedaquiline remains challenging given the diversity of variants observed.
FUNDING: Doris Duke Charitable Foundation, US National Institute of Allergy and Infectious Diseases, South African Medical Research Council, National Research

Foundation, Research Foundation Flanders, Stellenbosch University Faculty of Medicine Health Sciences, South African National Research Foundation, Swiss National Science Foundation, and Wellcome Trust.

DOI: 10.1016/S2666-5247(23)00172-6
PMID: 37931638

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

10. Tuberculosis Variant with Rifampin Resistance Undetectable by Xpert MTB/RIF, Botswana.

Emerg Infect Dis. 2023 Nov;29(11):2403-2406. doi: 10.3201/eid2911.230987.

Modongo C, Barilar I, Wang Q, Molefi T, Makhondo T, Niemann S, Shin SS.

GeneXpert MTB/RIF, a tool widely used for diagnosing tuberculosis, has limitations for detecting rifampin resistance in certain variants. We report transmission of a pre-extensively drug-resistant variant in Botswana that went undetected by GeneXpert. The public health impact of misdiagnosis emphasizes the need for comprehensive molecular testing to identify resistance and guide treatment.

DOI: 10.3201/eid2911.230987
PMCID: PMC10617350
PMID: 37877680 [Indexed for MEDLINE]

11. Community-based directly observed therapy is effective and results in better treatment outcomes for patients with multi-drug resistant tuberculosis in Uganda.

BMC Health Serv Res. 2023 Nov 13;23(1):1248. doi: 10.1186/s12913-023-10120-7.

Makabayi-Mugabe R(1)(2), Musaazi J(3), Zawedde-Muyanja S(3)(4), Kizito E(3), Fatta K(5), Namwanje-Kaweesi H(4), Turyahabwe S(6), Nkolo A(4).

BACKGROUND: Health facility-based directly observed therapy (HF DOT) is the main

strategy for the management of patients with drug-resistant tuberculosis (DR TB) in Uganda, however, this still yields sub-optimal treatment outcomes. We set out to assess the effectiveness of community-based directly observed therapy (CB DOT) for the treatment of DR TB in Uganda.
METHODS: Using a previously developed patient-centered model for CB DOT, we assigned community health workers (CHWs) as primary caregivers to patients diagnosed with DR TB. CHWs administered daily DOT to patients in their homes. Once a month, patients received travel vouchers to attend clinic visits for treatment monitoring. We assessed the effectiveness of this model using a quasi-experimental pre and post-study. From December 2020 to March 2022, we enrolled adult DR-TB patients on the CB DOT model. We collected retrospective data from patients who had received care using the HF DOT model during the year before the study started. The adjusted effect of CB DOT versus HF DOT on DR TB treatment success was estimated using modified Poisson regression model with robust cluster variance estimator.
RESULTS: We analyzed data from 264 DR TB patients (152 HF DOT, 112 CB DOT). The majority were males (67.8%) with a median age of 36 years (IQR 29 to 44 years). Baseline characteristics were similar across the comparison groups, except for educational level, regimen type, and organizational unit with age being borderline. The treatment success rate in the CB DOT group was 12% higher than that in the HF DOT (adjusted prevalence ratio (aPR)= 1.12 [95%CI 1.01, 1.24], P-value=0.03). Males were less likely to achieve treatment success compared to their female counterparts (aPR=0.87 [95% CI 0.78, 0.98], P-value=0.02). A total of 126 (47.7%) of 264 patients reported at least one adverse event. The HF DOT group had a higher proportion of patients with at least one adverse event compared to the CB DOT group (90/152 [59.2%] versus 36/112 [32.1], P-value<0.01). The model was acceptable among patients (93.6%) and health workers (94.1%).
CONCLUSIONS: CB DOT for DR-TB care is effective and results in better treatment outcomes than HF DOT. The cost-effectiveness of this model of care should be further evaluated.

DOI: 10.1186/s12913-023-10120-7
PMCID: PMC10644403
PMID: 37957610 [Indexed for MEDLINE]

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

12. Real-world impact of the fixed-dose combination on improving treatment outcomes of drug-susceptible tuberculosis: a comparative study using multiyear national tuberculosis patient data.

BMJ Open Respir Res. 2023 Nov;10(1):e001758. doi: 10.1136/bmjresp-2023-001758.

Ki MS(#)(1), Jeong D(#)(2), Kang HY(3), Choi H(4), Sohn H(#)(2), Kang YA(#)(5)(6).

BACKGROUND: The fixed-dose combination (FDC) for first-line antituberculosis (TB) treatment has long been a standard practice worldwide; however, there is limited evidence on whether the use of FDC improves long-term treatment outcomes in the real-world setting.
METHODS: We identified 32 239 newly diagnosed patients with drug-susceptible (DS) TB in 2015 and 2016 who had been prescribed FDC or non-FDC TB treatment from a multiyear (2013-2018) national TB cohort database that linked the Korean National Tuberculosis Surveillance System, the National Health Insurance Database and the Health Insurance Review and Assessment Service database. Inverse probability of treatment weighting (IPTW) with a propensity score was used to control for differences in patient characteristics between 5926 patients with TB treated with FDC and 26 313 patients with non-FDC. Multivariable logistic regression analyses were performed to assess for the factors influencing treatment outcomes between the two groups.
RESULTS: After IPTW, new patients with DS-TB treated with FDC had higher treatment completion rate (83.9% vs 78.9%, p<0.01) and lower death rates (8.2% vs 9.8%, p<0.01) with similar TB recurrence rate (2.3% vs 2.4%) compared with those treated with non-FDC. In multivariable analyses, FDC use had higher odds treatment completion (adjusted OR 1.45; 95% CI 1.34 to 1.56). Patients with TB with younger age (relative to 70+ age) and higher income level had higher odds for treatment completion. Use of FDC did not influence TB recurrence after treatment completion (adjusted HR 0.94; 95% CI 0.77 to 1.16). The acquired drug resistance rate was similar between the two groups (drug-resistant TB in FDC 4.7% vs non-FDC 5.3%; p=0.80).
CONCLUSION: In Korea, prescription of FDC to treat newly diagnosed patients with DS TB improved patient's treatment completion. Use of FDC did not increase the risks of TB recurrence or development of drug resistance.

DOI: 10.1136/bmjresp-2023-001758
PMCID: PMC10626786
PMID: 37918950 [Indexed for MEDLINE]

Conflict of interest statement: Competing interests: None declared.

13. Major adverse cardiovascular events and hyperuricemia during tuberculosis treatment.

PLoS One. 2023 Nov 16;18(11):e0294490. doi: 10.1371/journal.pone.0294490. eCollection 2023.

Shin HJ(1)(2), Yoon JY(1), Na YO(1), Lee JK(1), Kho BG(1), Kim TO(1)(2), Kim YI(1)(2), Lim SC(1)(2), Jeong SH(1), Kwon YS(1)(2).

BACKGROUND: Hyperuricemia is common during tuberculosis (TB) treatment, especially in association with pyrazinamide (PZA). This study investigated the relationship between major adverse cardiovascular events (MACEs) and hyperuricemia during TB treatment.
METHODS: We conducted a single-center retrospective cohort study. From January 2010 through June 2017, we assessed all consecutive TB patients at Chonnam National University Hospital in South Korea. Hyperuricemia was defined as serum uric acid levels exceeding 7.0 mg/dL (men) and 6.0 mg/dL (women).
RESULTS: Of the 1,143 patients included, PZA was administered to 1,081 (94.6%), and hyperuricemia was detected in 941 (82.3%). Eight patients experienced MACEs. Multivariate analysis using logistic regression indicated that prior ischemic heart disease was associated with MACE development (OR,14.087; 95% CI,3.304-60.061; P < 0.000), while hyperuricemia was not (OR, 1.505; 95% CI, 0.184-12.299; P = 0.703). For patients without drug-resistant TB, the absence of hyperuricemia was associated with higher mortality (OR, 2.609; 95% CI, 1.066-6.389; P = 0.036), whereas hyperuricemia was associated with less worse outcomes (OR,0.316; 95% CI,0.173-0.576; P < 0.000).
CONCLUSIONS: Although most patients treated with PZA developed hyperuricemia, it was not associated with MACE development. Hyperuricemia during TB treatment was associated with better outcomes, possibly due to consistent adherence to TB treatment.

DOI: 10.1371/journal.pone.0294490
PMCID: PMC10653473
PMID: 37972037 [Indexed for MEDLINE]

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

14. Deep learning on longitudinal CT scans: automated prediction of treatment outcomes in hospitalized tuberculosis patients.

iScience. 2023 Oct 23;26(11):108326. doi: 10.1016/j.isci.2023.108326.
eCollection 2023 Nov 17.

Nijiati M(1), Guo L(2), Tuersun A(1), Damola M(1), Abulizi A(1), Dong J(1), Xia L(2), Hong K(2), Zou X(3).

Three deep learning (DL)-based prediction models (PMs) using longitudinal CT images were developed to predict tuberculosis (TB) treatment outcomes. The internal dataset consists of 493 bacteriologically confirmed TB patients who completed the anti-tuberculosis treatment with three-time CT scans, including a pretreatment CT scan and two follow-up CT scans. PM1 was trained using only pretreatment CT scans, and PM2 and PM3 were developed by adding follow-up scans. An independent testing was performed on external dataset comprising 86 TB patients. The area under the curve for classifying success and drug-resistant (DR)-TB was improved on both internal (0.609 vs. 0.625 vs. 0.815) and external (0.627 vs. 0.705 vs. 0.735) dataset by adding follow-up scans. The accuracy and F1-score also showed an increasing tendency in the external test. Regular follow-up CT scans can aid in the treatment prediction, and special attention should be given to early intensive phase of treatment to identify high-risk DR-TB patients.

DOI: 10.1016/j.isci.2023.108326
PMCID: PMC10641748
PMID: 37965132

Conflict of interest statement: L.G. Activities related to the present article: disclosed no relevant relationships. Activities not related to the present article: disclosed employee of Shenzhen Zhiying Medical Imaging. Other relationships: disclosed no relevant relationships. L.X. Activities related to the present article: disclosed no relevant relationships. Activities not related to the present article: disclosed employee of Shenzhen Zhiying Medical Imaging. K.H. Activities related to the present article: disclosed no relevant relationships. Activities not related to the present article: disclosed employee of Shenzhen Zhiying Medical Imaging. Other relationships: disclosed no relevant relationships.

15. Organisation of care for people receiving drug-resistant tuberculosis treatment in South Africa: a mixed methods study.

BMJ Open. 2023 Nov 17;13(11):e067121. doi: 10.1136/bmjopen-2022-067121.

Dickson L(1), Le Roux SR(1), Mitrani L(1), Hill J(2), Jassat W(3), Cox H(1)(4), Mlisana K(5), Black J(6), Loveday M(7), Grant A(2)(8), Kielmann K(9)(10), Ndjeka N(11)(12), Moshabela M(12), Nicol M(13)(14).

OBJECTIVES: Treatment for multidrug-resistant/rifampicin-resistant tuberculosis (MDR/RR-TB) is increasingly transitioning from hospital-centred to community-based care. A national policy for decentralised programmatic MDR/RR-TB care was adopted in South Africa in 2011. We explored variations in the implementation of care models in response to this change in policy, and the implications of these variations for people affected by MDR/RR-TB.
DESIGN: A mixed methods study was done of patient movements between healthcare facilities, reconstructed from laboratory records. Facility visits and staff interviews were used to determine reasons for movements.
PARTICIPANTS AND SETTING: People identified with MDR/RR-TB from 13 high-burden districts within South Africa.
OUTCOME MEASURES: Geospatial movement patterns were used to identify organisational models. Reasons for patient movement and implications of different organisational models for people affected by MDR/RR-TB and the health system were determined.
RESULTS: Among 191 participants, six dominant geospatial movement patterns were identified, which varied in average hospital stay (0-281 days), average patient distance travelled (12-198 km) and number of health facilities involved in care (1-5 facilities). More centralised models were associated with longer delays to treatment initiation and lengthy hospitalisation. Decentralised models facilitated family-centred care and were associated with reduced time to treatment and hospitalisation duration. Responsiveness to the needs of people affected by MDR/RR-TB and health system constraints was achieved through implementation of flexible models, or the implementation of multiple models in a district.
CONCLUSIONS: Understanding how models for organising care have evolved may assist policy implementers to tailor implementation to promote particular patterns of care organisation or encourage flexibility, based on patient needs and local health system resources. Our approach can contribute towards the development of a health systems typology for understanding how policy-driven models of service delivery are implemented in the context of variable resources.

DOI: 10.1136/bmjopen-2022-067121
PMID: 37977868

Conflict of interest statement: Competing interests: None declared.

16. Computed Tomography Manifestations in Patients with Rifampin Primary Drug-Resistant Tuberculosis in an Infectious Disease Hospital in the Yi Autonomous Prefecture, China.

Int J Gen Med. 2023 Nov 6;16:5109-5118. doi: 10.2147/IJGM.S428962. eCollection 2023.

Wang T(#)(1)(2), Yang Q(#)(3), Gao Y(2), Zhang R(2), Zhou C(2), Kong W(1), Zhang G(1), Chen X(4), Pu H(1), Shang L(1).

PURPOSE: This study aimed to investigate clinical features and computed tomography (CT) manifestations of rifampicin primary drug-resistant pulmonary tuberculosis in Liangshan Yi Autonomous Prefecture.
PATIENTS AND METHODS: A total of 100 inpatients with confirmed primary rifampicin-resistant pulmonary tuberculosis were recruited from January 2020 to December 2022 at an infectious disease hospital located in the Liangshan Yi Autonomous Prefecture. Additionally, 100 inpatients with confirmed drug-susceptible pulmonary tuberculosis during the same period were matched to the rifampicin-resistant group based on gender, age, and ethnicity. The clinical characteristics of the two groups were recorded separately. Furthermore, the CT manifestations in these patients were independently analyzed by three radiologists.
RESULTS: The results showed that comorbid diabetes mellitus was more prevalent in the drug-resistant tuberculosis (DR-TB) group than in the drug-susceptible tuberculosis (DS-TB) group (9% vs 0%, p=0.0032). In terms of imaging presentation, DR-TB patients exhibited a higher frequency of calcifications (55% vs 35.00%, p=0.0068), greater median number of cavities (5 vs 2, p=0.0027), and larger maximum cavity diameter (52.08±25.55 mm vs 42.72±17.48 mm, p=0.0097). Additionally, bilateral involvement was more common in DR-TB patients at the site of the lesion (89% vs 76%, p=0.0246), with a higher prevalence in the right middle (82% vs 68%, p=0.0332), right lower (82% vs 68%, p=0.0332), left upper (91% vs 77%, p=0.0113), and left lower lobes (92% vs 66%, p<0.0001). Conversely, the involvement of only one lobe was less frequent in patients with DR-TB than in those with DS-TB (4% vs 13%, p=0.0398), whereas the involvement of all five lobes was more common (68% vs 51%, p=0.0209).
CONCLUSION: Patients with DR-TB exhibit a higher prevalence of severe imaging manifestations, highlighting the importance of CT in the early detection and diagnosis of DR-TB.

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PMCID: PMC10637220
PMID: 37954652

Conflict of interest statement: All authors declare no conflicts of interest for this work.

17. Successful treatment of tuberculous meningitis in an Indian female under hemodialysis therapy.

CEN Case Rep. 2023 Nov;12(4):341-346. doi: 10.1007/s13730-022-00771-6. Epub 2023 Jan 8.

Oshima S(1), Sakuragi M(1), Morita H(1), Oka Y(2), Tabu H(2), Marumo S(3), Suzuki H(1), Tsukamoto T(4).

Hemodialysis is a well-known risk factor for severe infection by putting patients under an immunocompromised state. Such patients are prone to opportunistic pathogen and present with atypical manifestations during infection. Tuberculous meningitis is a central nervous system infection of Mycobacterium tuberculosis, accounting for the highest mortality of all forms of tuberculosis. In fact, the mortality rate of tuberculous meningitis in hemodialysis patients is extremely poor because early clinical diagnosis is difficult. Here, we report a case of tuberculous meningitis in a 61-year-old Indian hemodialysis patient, who presented with fever of unknown origin and was successfully treated with empiric treatment with standard four-drug regimen against tuberculosis. Comprehensive screening of the origin of fever revealed only the positive results of interferon-gamma release assay, which led us to initiate an empiric therapy for tuberculosis, before making a definitive diagnosis by cerebrospinal fluid nested PCR. Soon after the initiation of the treatment, the fever immediately abated. Although the patient experienced a single episode of paradoxical worsening and severe liver injury, she recovered well without any complications. This report provides a clinical course of the disease in a hemodialysis patient, highlighting the importance of early clinical diagnosis and rapid initiation of empirical tuberculosis treatment.

DOI: 10.1007/s13730-022-00771-6
PMCID: PMC10620348
PMID: 36611090 [Indexed for MEDLINE]

Conflict of interest statement: The authors have declared that no conflict of interest exists.

18. Molecular characterization of genetic mutations with fitness loss in pulmonary tuberculosis patients associated with HIV co-infection in Northwest Amhara, Ethiopia.

SAGE Open Med. 2023 Nov 3;11:20503121231208266. doi: 10.1177/20503121231208266. eCollection 2023.

Seid A(1)(2), Kassa M(3), Girma Y(3), Dereb E(3), Nureddin S(4), Abebe A(3), Berhane N(2).

OBJECTIVES: Molecular approaches to identifying resistance-conferring mutations suggest a revolution in the field of tuberculosis. The aim of the study was to determine the association between resistance-conferring mutations with fitness loss in Mycobacterium tuberculosis clinical isolates and HIV co-infection in the Amhara region of Ethiopia.
METHODS: A laboratory-based cross-sectional study was conducted between September 2022 and June 2023. A line probe assay was performed on 146 culture-positive clinical isolates. Logistic regression analysis was used to measure the strength of the association between the drug-resistance-conferring mutations with fitness loss in M. tuberculosis isolates and tuberculosis/HIV co-infection. A p-value $\leqslant 0.05$ was considered statistically significant.
RESULTS: A total of 11 distinct mutations at four genetic loci among 19 resistant isolates were detected. The frequency of rifampicin, isoniazid, and fluoroquinolones resistance-conferring mutations was identified in 12 (8.2%), 17 (11.6%), and 2 (1.4%) of the isolates, respectively. The most prominent specific mutations were S450L (5/9, 55.6%), S315T (11/11, 100%), C-15T (4/4, 100%), and D94G (1/1, 100%). Double mutations were observed in 10 (52.6%) multidrug-resistant tuberculosis isolates; the most common were detected in both the rpoB and katG genes (8/10, 80.0%). The HIV-co-infected tuberculosis patients carried a higher proportion of low fitness of non-rpoB S450L variants than those tuberculosis patients without HIV (80.0% vs 14.3%) and showed a significant association (cOR = 0.042, 95% CI: 0.002-0.877, p = 0.041), but not with the low fitness of non-katG S315T variants (cOR = 3.00, 95% CI: 0.348-25.870, p = 0.318).
CONCLUSION: This study provides valuable information on the genetic variants with fitness loss associated with HIV co-infection, but requires further whole-genome-based mutation analysis.

DOI: 10.1177/20503121231208266
PMCID: PMC10625730
PMID: 37933292

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

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

Microbiol Spectr. 2023 Nov 16:e0256223. doi: 10.1128/spectrum.02562-23. Online ahead of print.

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

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

DOI: 10.1128/spectrum.02562-23
PMID: 37971428

<u>Pub Med Non-Open Access</u>

20. Linezolid optic neuropathy.

Curr Opin Ophthalmol. 2023 Nov 1;34(6):481-486. doi: 10.1097/ICU.0000000000000995. Epub 2023 Aug 21.

Miller HV(1), Cao AA(2), McClelland CM(1)(3), Lee MS(1)(3).

PURPOSE OF REVIEW: In this article, we reviewed 67 reported cases of linezolid optic neuropathy and describe the common characteristics and expectations for recovery with an emphasis on recent findings in the literature.
RECENT FINDINGS: Linezolid classically causes a reversible, duration-dependent optic neuropathy. However, in our review, we found only 66.7% of patients recovered complete visual function. Vision loss most commonly affected visual acuity followed by visual field and color vision. We also found patients taking higher doses of linezolid experienced full recovery less often, suggesting a dose-dependent component of linezolid optic neuropathy. Linezolid use has increased in frequency and duration, especially in the treatment of drug-resistant tuberculosis, and data indicate that these patients experience lower rates of complete vision recovery compared with patients taking linezolid for other indications.
SUMMARY: Linezolid is an effective medication for treating drug-resistant infections; however, it may result in optic neuropathy. It is reasonable for patients on linezolid to undergo screening examinations, especially those on higher doses or for prolonged duration of therapy.

DOI: 10.1097/ICU.0000000000000995
PMID: 37603423 [Indexed for MEDLINE]

21. Successful Multidrug-Resistant Tuberculosis Treatment Without HIV Viral Suppression: A Missed Opportunity.

J Acquir Immune Defic Syndr. 2023 Nov 1;94(3):253-261. doi: 10.1097/QAI.0000000000003268.

Geiger K(1)(2), Patil A(2), Budhathoki C(1), Dooley KE(3), Lowensen K(2), Ndjeka N(4)(5), Ngozo J(6), Farley JE(1)(2).

BACKGROUND: Coinfection with multidrug-resistant tuberculosis (MDR-TB) and HIV is common, but few published studies examine how undergoing MDR-TB treatment affects HIV disease indicators.
METHODS: Using data from a nested, retrospective cohort of people with HIV (PWH) and successful MDR-TB treatment outcomes, we built multivariable regression models to explore correlates of HIV viral suppression at MDR-TB treatment completion.
RESULTS: Among 531 PWH successfully treated for MDR-TB, mean age was 37.4 years (SD 10.2, interquartile range 30-43), 270 (50.8%) were male, 395 (74.4%) were virally suppressed at MDR-TB outcome, and 259 (48.8%) took bedaquiline. Older

age (adjusted odds ratio [aOR] 1.04, 95% confidence interval [CI]: 1.01 to 1.06) increased odds of viral suppression, while having a prior TB episode (aOR 0.45, 95% CI: 0.31 to 0.64), having a detectable viral load at MDR-TB treatment initiation (aOR 0.17, 95% CI: 0.09 to 0.30), living in a township (aOR 0.49, 95% CI: 0.28 to 0.87), and being changed from efavirenz-based antiretroviral therapy (ART) to a protease inhibitor due to bedaquiline usage (aOR 0.19, 95% CI: 0.04 to 0.82) or not having an ART change while on bedaquiline (aOR 0.29, 95% CI: 0.11 to 0.75) lowered odds of viral suppression. Changing from efavirenz to nevirapine due to bedaquiline usage did not significantly affect odds of viral suppression (aOR 0.41, 95% CI: 0.16 to 1.04).
CONCLUSIONS: Increased pill burden and adverse treatment effects did not significantly affect HIV viral suppression while switching ART to a protease inhibitor to accommodate bedaquiline or not changing ART while taking bedaquiline did, suggesting that PWH and MDR-TB may benefit from additional support if they must switch ART.

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PMCID: PMC10592374
PMID: 37757847 [Indexed for MEDLINE]

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

22. Treatment Outcomes in Multidrug-Resistant Tuberculosis During Pregnancy.

Clin Infect Dis. 2023 Nov 1:ciad594. doi: 10.1093/cid/ciad594. Online ahead of print.

Liu X(1), Xia L(1), Wang X(2), Huang Z(2), Lu S(1)(2).

DOI: 10.1093/cid/ciad594
PMID: 37930787

Conflict of interest statement: Potential conflicts of interest. The authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

23. Exploring and exploiting the host cell autophagy during Mycobacterium tuberculosis infection.

Eur J Clin Microbiol Infect Dis. 2023 Nov;42(11):1297-1315. doi: 10.1007/s10096-023-04663-0. Epub 2023 Sep 23.

Nagdev PK(1), Agnivesh PK(1), Roy A(1), Sau S(1), Kalia NP(2).

Tuberculosis, caused by Mycobacterium tuberculosis, is a fatal infectious disease that prevails to be the second leading cause of death from a single infectious agent despite the availability of multiple drugs for treatment. The current treatment regimen involves the combination of several drugs for 6 months that remain ineffective in completely eradicating the infection because of several drawbacks, such as the long duration of treatment and the side effects of drugs causing non-adherence of patients to the treatment regimen. Autophagy is an intracellular degradative process that eliminates pathogens at the early stages of infection. Mycobacterium tuberculosis's unique autophagy-blocking capability makes it challenging to eliminate compared to usual pathogens. The present review discusses recent advances in autophagy-inhibiting factors and mechanisms that could be exploited to identify autophagy-inducing chemotherapeutics that could be used as adjunctive therapy with the existing first-line anti-TB agent to shorten the duration of therapy and enhance cure rates from multidrug-resistant tuberculosis (MDR-TB) and extreme drug-resistant tuberculosis (XDR-TB).

DOI: 10.1007/s10096-023-04663-0
PMID: 37740791

24. Pre-extensively drug-resistant tuberculosis among pulmonary multidrug-resistant tuberculosis patients in Eastern Nigeria.

Lung India. 2023 Nov-Dec;40(6):492-495. doi: 10.4103/lungindia.lungindia_337_23.

Nwachukwu NO(1), Ulasi AE(2), Okoronkwo CU(3), Unegbu VN(4).

BACKGROUND: Pre-extensively drug-resistant tuberculosis (Pre-XDR-TB), an emerging form of drug-resistant tuberculosis, is challenging efforts at tuberculosis control, leading to treatment failure among multidrug-resistant tuberculosis (MDR-TB) patients and progression to extensively drug-resistant tuberculosis (XDR-TB). We determined the rate of Pre-XDR-TB among multidrug-resistant patients in Southeast, Nigeria.
METHODS: A prospective laboratory-based study was carried out at the South East Zonal Tuberculosis Reference Laboratory from January 2021 to December 2021. Second-line drug (SLD) resistance was performed on 225 sputum samples of multidrug-resistant patients prior to treatment initiation using GenoType MTBDRsl genotypic drug susceptibility testing (DST) method.

RESULTS: The rate of Pre-XDR-TB among 225 MDR-TB cases was 3.1%. Fluoroquinolone-resistant Pre-XDR-TB was observed (100%) in previously treated tuberculosis cases. Only one (0.4%) case showed resistance to both fluoroquinolone (FQ) and one second-line injectable drug (XDR-TB). The extensively drug-resistant case observed was a de-novo resistance. Exactly 0.9% of the multidrug-resistant cases showed resistance to second-line injectables. CONCLUSION: The prevalence of Pre-XDR-TB among MDR-TB cases was high. There is need for rapid detection of Pre-XDR-TB among MDR-TB cases before treatment initiation.

DOI: 10.4103/lungindia.lungindia_337_23
PMID: 37961955

25. Cotreatment With Clofazimine and Rapamycin Eliminates Drug-Resistant Tuberculosis by Inducing Polyfunctional Central Memory T-Cell Responses.

J Infect Dis. 2023 Nov 2;228(9):1166-1178. doi: 10.1093/infdis/jiad214.

Singh DK(1)(2), Bhaskar A(1), Pahuja I(1), Shaji A(1), Moitra B(2), Shi Y(3), Dwivedi VP(1), Das G(2).

Mycobacterium tuberculosis, the causative agent of tuberculosis, is acquiring drug resistance at a faster rate than the discovery of new antibiotics. Therefore, alternate therapies that can limit the drug resistance and disease recurrence are urgently needed. Emerging evidence indicates that combined treatment with antibiotics and an immunomodulator provides superior treatment efficacy. Clofazimine (CFZ) enhances the generation of T central memory (TCM) cells by blocking the Kv1.3+ potassium channels. Rapamycin (RAPA) facilitates M. tuberculosis clearance by inducing autophagy. In this study, we observed that cotreatment with CFZ and RAPA potently eliminates both multiple and extensively drug-resistant (MDR and XDR) clinical isolates of M. tuberculosis in a mouse model by inducing robust T-cell memory and polyfunctional TCM responses. Furthermore, cotreatment reduces the expression of latency-associated genes of M. tuberculosis in human macrophages. Therefore, CFZ and RAPA cotherapy holds promise for treating patients infected with MDR and XDR strains of M. tuberculosis.

DOI: 10.1093/infdis/jiad214
PMID: 37290049 [Indexed for MEDLINE]

26. Discovery, Synthesis, and Optimization of 1,2,4-Triazolyl Pyridines Targeting Mycobacterium tuberculosis.

ACS Infect Dis. 2023 Nov 10;9(11):2282-2298. doi: 10.1021/acsinfecdis.3c00341. Epub 2023 Oct 3.

Berida T(1), McKee SR(2), Chatterjee S(1), Manning DL(1), Li W(3), Pandey P(4), Tripathi SK(4), Mreyoud Y(2), Smirnov A(2), Doerksen RJ(1), Jackson M(3), Ducho C(5), Stallings CL(2), Roy S(1).

The rise in multidrug resistant tuberculosis cases underscores the urgent need to develop new treatment strategies for tuberculosis. Herein, we report the discovery and synthesis of a new series of compounds containing a 3-thio-1,2,4-triazole moiety that show inhibition of Mycobacterium tuberculosis (Mtb) growth and survival. Structure-activity relationship studies led us to identify several potent analogs displaying low micromolar to nanomolar inhibitory activity, specifically against Mtb. The potent analogs demonstrated no cytotoxicity in mammalian cells at over 100 times the effective concentration required in Mtb and were bactericidal against Mtb during infection of macrophages. In the exploratory ADME investigations, we observed suboptimal ADME characteristics, which prompted us to identify potential metabolic liabilities for further optimization. Our preliminary investigations into the mechanism of action suggest that this series is not engaging the promiscuous targets that arise from many phenotypic screens. We selected for resistant mutants with the nanomolar potent nitro-containing compound 20 and identified resistant isolates with mutations in genes required for coenzyme F420 biosynthesis and the nitroreductase Ddn. This suggests that the aromatic nitro-1,2,4-triazolyl pyridines are activated by F420-dependent Ddn activity, similar to the nitro-containing TB drug pretomanid. We were able to circumvent the requirement for F420-dependent Ddn activity using compounds that contained non-nitro groups, identifying a key feature to be modified to avoid this predominant resistance mechanism. These studies provide the foundation for the development of a new class of 1,2,4-triazole compounds for the treatment of tuberculosis.

DOI: 10.1021/acsinfecdis.3c00341
PMID: 37788674 [Indexed for MEDLINE]

27. In vitro activity of tubercidin against Mycobacterium tuberculosis and nontuberculosis Mycobacteria.

J Med Microbiol. 2023 Nov;72(11). doi: 10.1099/jmm.0.001763.

Sun Q(1), Liao X(2), Yan J(2), Jiang G(1), Huo F(1), Wang G(2), Li H(3)(4).

Tubercidin is an adenosine analogue that has been shown to exhibit good activity against some tumours and parasites. In this study, the in vitro activity of tubercidin was evaluated against Mycobacterium tuberculosis (Mtb) and nontuberculosis Mycobacteria (NTM). For determining the MICs of tubercidin, 23 fully drug-sensitive (DS) Mtb strains, 33 multi-drug resistance tuberculosis (MDR-TB) strains, 29 pre-extensively drug-resistant tuberculosis (pre-XDR-TB) strains, 21 extensively drug-resistant tuberculosis (XDR-TB) strains, 17 rapidly growing mycobacteria (RGM) and nine slowly growing mycobacteria (SGM) references strains were tested by microplate-based Alamar Blue assay (MABA) method. The results indicate that tubercidin has high in vitro activity against some drug-resistance Mtb strains and NTM reference strains, which warrants further investigation on the actions of tubercidin and its derivatives as potential drugs for mycobacterial infections.

DOI: 10.1099/jmm.0.001763
PMID: 37910006 [Indexed for MEDLINE]

28. Microbial glycosylation of antitubercular agent chlorflavonin.

J Biosci Bioeng. 2023 Nov;136(5):366-373. doi: 10.1016/j.jbiosc.2023.09.005. Epub 2023 Sep 23.

Ren J(1), Zhan J(2).

Flavonoids have shown health-benefiting properties, such as antioxidative and anti-inflammatory activities, and are commonly used as nutraceuticals and pharmaceuticals. Although flavonoids are predominantly identified from plants, several filamentous fungal species have also been reported to produce bioactive flavonoids, including chlorflavonin from Aspergillus candidus, a novel halogenated flavonoid with potent antifungal and antitubercular (anti-TB) activities. Unfortunately, the low water-solubility of this molecule may hinder its bioavailability. Glycosylation is an effective method to enhance the polarity of natural products and alter their physicochemical properties. This work focuses on the development of novel water-soluble chlorflavonin derivatives to combat the threat of drug-resistant tuberculosis. In this study, we first increased the production titer of chlorflavonin in A. candidus NRRL 5214 by optimizing the fermentation and purification processes. Next, chlorflavonin-5-O-β-d-glucuronopyranoside (1) and chlorflavonin-7-O-4″-O-methyl-β-d-glucopyranoside (2) were produced from chlorflavonin using Streptomyces chromofuscus ATCC 49982 and Beauveria bassiana ATCC 7159, respectively. Compared to chlorflavonin (4.38 ± 0.54 mg/L in water), the water solubility of the two new glycosides was determined to be 117.86 ± 4.81 mg/L (1) and 124.34 ± 9.13 mg/L (2), respectively. This study provides a promising method to create water-soluble glycosides of chlorflavonin for the

development of novel anti-TB drugs.

DOI: 10.1016/j.jbiosc.2023.09.005
PMID: 37743150

29.New Insights into Biomarkers for Evaluating Therapy Efficacy in Pulmonary Tuberculosis: A Narrative Review.

Infect Dis Ther. 2023 Nov 8. doi: 10.1007/s40121-023-00887-x. Online ahead of print.

Zhang F(#)(1)(2), Zhang F(#)(2), Dong Y(1), Li L(3)(4), Pang Y(5).

Evaluating therapy efficacy is crucial for patients with tuberculosis (TB), especially those with drug-resistant tuberculosis (DR-TB). The World Health Organization currently recommends sputum smear and culture as the standard methods for evaluating pulmonary tuberculosis (PTB) therapy efficacy. However, these approaches have limitations including low sensitivity, lengthy culture periods, and susceptibility to contamination. There is an urgent need for dependable biomarkers to evaluate therapy efficacy in patients with PTB. Numerous new biomarkers of Mycobacterium tuberculosis (MTB) and the host have been used in recent studies to evaluate PTB therapy efficacy. A systematic review and update of these biomarkers can facilitate the discovery of novel biomarkers and assessment models, as well as provide a solid scientific basis for alternative indicators of evaluating therapy efficacy. In this review we summarize the recent advancements and limitations of biomarkers used to monitor therapy efficacy, highlighting the importance of utilizing a combination of biomarkers. Although some biomarkers have potential in evaluating the efficacy of therapy in patients with PTB, they also have some limitations. Further research, validation, and optimization are required to identify the most reliable and effective alternative biomarkers and apply them to clinical practice.

DOI: 10.1007/s40121-023-00887-x
PMID: 37938418

30. Design and synthesis of benzo[b]thiophene-based hybrids as novel antitubercular agents against MDR/XDR Mycobacterium tuberculosis.

Arch Pharm (Weinheim). 2023 Nov 9:e2300529. doi: 10.1002/ardp.202300529. Online ahead of print.

Al-Warhi T(1), Rashad NM(2), Almahli H(3), Abdel-Aziz MM(4), Elsayed ZM(2), Shahin MI(5), Eldehna WM(6).

In an effort to support the global fight against tuberculosis (TB), which is widely recognized as the most lethal infectious disease worldwide, we present the design and synthesis of new benzo[b]thiophene-based hybrids as promising candidates for the management of multidrug-resistant (MDR)/extensively drug-resistant (XDR) Mycobacterium tuberculosis. The isatin motif was incorporated into the target hybrids as it represents a privileged scaffold in antitubercular drug discovery. Since lipophilicity plays a pivotal role in the anti-TB agents' activity, the lipophilicity of the target hybrids was manipulated via the development of two series of N-1 methyl and N-1 benzyl substituted isatins (6a-h and 9a-h, respectively). Screening of the target hybrids was first performed against drug-sensitive M. tuberculosis (ATCC 25177). The structure-activity relationship outputs highlighted that incorporation of 3-unsubstituted benzo[b]thiophene and 5-methoxy isatin moieties was favorable for the antimycobacterial activity. Thereafter, the most potent molecules (6b-h, 9c-e, and 9h) were evaluated against the resistant strains MDR-TB (ATCC 35822) as well as against XDR-TB (RCMB 2674) where they displayed promising activity. To evaluate the safety of the target hybrids, an sulforhodamine B assay was conducted to determine their possible cytotoxic effects on VERO cells.

DOI: 10.1002/ardp.202300529
PMID: 37946574

31. Investigation of efflux pump genes in isoniazid resistant Mycobacterium tuberculosis isolates.

Indian J Med Microbiol. 2023 Nov-Dec;46:100428. doi: 10.1016/j.ijmmb.2023.100428. Epub 2023 Jul 19.

Kaya H(1), Ersoy L(2), Ülger M(3), Bozok T(4), Aslan G(5).

BACKGROUND: Tuberculosis (TB) is one of the most important infectious diseases worldwide. Resistance to antituberculosis drugs develops because of genetic mutations that render drug-activating enzymes inactive, changes in cell wall permeability, and increased expression of efflux pump genes and also combination therapy with efflux pump inhibitors may be more effective in drug-resistant TB patients.

AIMS: To investigate the effect of verapamil (VR) on isonicotinic acid hydrazide (INH) resistance and the expression of 21 efflux pump genes in INH monoresistant MTBC clinical isolates.
STUDY DESIGN: In vitro study.
METHODS: In our mycobacteriology laboratory, 10 INH monoresistant and 10 primary anti-TB drug-susceptible MTBC clinical isolates were selected. Drug susceptibilities for INH and VR were studied by resazurin microtiter plate method and minimum inhibitory concentration (MIC) was determined. Additionally, mRNA gene expressions were investigated by quantitative Real Time Polymerase Chain Reaction for 21 efflux gene regions.
RESULTS: While no change was observed in INH MICs of susceptible isolates under VR effect, 6 (60%) of the 10 INH-resistant isolates showed a decrease of less than one dilution in INH MIC under VR effect. VR significantly reduced resistance in resistant isolates ($p < 0.05$). INH monoresistant MTBC isolates showed a 2.85-fold expression increase in the Rv1634 region of the Major Facilitator Superfamily efflux family under INH stress ($p = 0.029$). No statistically significant change was observed in other efflux gene regions. Herein, increased expression was observed in the Rv1634 region, consistent with other studies in the literature, and this was associated with drug resistance. No significant change in expression was detected in other gene regions.
CONCLUSION: The effect of efflux pump inhibitor VR on INH MIC levels is promising for the treatment of resistant TB. However, studies with more resistant strains are needed to evaluate the efficacy of efflux pump genes.

DOI: 10.1016/j.ijmmb.2023.100428
PMID: 37945121 [Indexed for MEDLINE]

32. Global status of phenotypic pyrazinamide resistance in Mycobacterium tuberculosis clinical isolates: an updated systematic review and meta-analysis.

J Chemother. 2023 Nov;35(7):583-595. doi: 10.1080/1120009X.2023.2214473. Epub 2023 May 21.

Wang Z(1), Tang Z(1), Heidari H(2), Molaeipour L(3), Ghanavati R(4), Kazemian H(5), Koohsar F(6), Kouhsari E(6)(7).

Pyrazinamide (PZA) is an essential first-line tuberculosis drug for its unique mechanism of action active against multidrug-resistant-TB (MDR-TB). Thus, the aim of updated meta-analysis was to estimate the PZA weighted pooled resistance (WPR) rate in M. tuberculosis isolates based on publication date and WHO regions. We systematically searched the related reports in PubMed, Scopus, and

Embase (from January 2015 to July 2022). Statistical analyses were performed using STATA software. The 115 final reports in the analysis investigated phenotypic PZA resistance data. The WPR of PZA was 57% (95% CI 48-65%) in MDR-TB cases. According to the WHO regions, the higher WPRs of PZA were reported in the Western Pacific (32%; 95% CI 18-46%), South East Asian region (37%; 95% CI 31-43%), and the Eastern Mediterranean (78%; 95% CI 54-95%) among any-TB patients, high risk of MDR-TB patients, and MDR-TB patients, respectively. A negligible increase in the rate of PZA resistance were showed in MDR-TB cases (55% to 58%). The rate of PZA resistance has been rising in recent years among MDR-TB cases, underlines the essential for both standard and novel drug regimens development.

DOI: 10.1080/1120009X.2023.2214473
PMID: 37211822 [Indexed for MEDLINE]

33. Long-term outcomes after tuberculosis for people with HIV in eastern Europe.

AIDS. 2023 Nov 1;37(13):1997-2006. doi: 10.1097/QAD.0000000000003670. Epub 2023 Jul 27.

Kraef C(1)(2)(3), Bentzon A(1), Roen A(1)(4), Bolokadze N(5), Thompson M(6), Azina I(7), Tetradov S(8), Skrahina A(9), Karpov I(10), Mitsura V(11), Paduto D(12), Trofimova T(13), Borodulina E(14), Mocroft A(1)(4), Kirk O(1)(2), Podlekareva DN(1)(15); TB:HIV study group.

BACKGROUND: Eastern Europe has a high burden of tuberculosis (TB)/HIV coinfection with high mortality shortly after TB diagnosis. This study assesses TB recurrence, mortality rates and causes of death among TB/HIV patients from Eastern Europe up to 11 years after TB diagnosis.
METHODS: A longitudinal cohort study of TB/HIV patients enrolled between 2011 and 2013 (at TB diagnosis) and followed-up until end of 2021. A competing risk regression was employed to assess rates of TB recurrence, with death as competing event. Kaplan-Meier estimates and a multivariable Cox-regression were used to assess long-term mortality and corresponding risk factors. The Coding Causes of Death in HIV (CoDe) methodology was used for adjudication of causes of death.
RESULTS: Three hundred and seventy-five TB/HIV patients were included. Fifty-three (14.1%) were later diagnosed with recurrent TB [incidence rate 3.1/100 person-years of follow-up (PYFU), 95% confidence interval (CI) 2.4-4.0] during a total follow-up time of 1713 PYFU. Twenty-three of 33 patients with data on drug-resistance (69.7%) had multidrug-resistant (MDR)-TB. More than half with recurrent TB (n = 30/53, 56.6%) died. Overall, 215 (57.3%) died during the follow-up period, corresponding to a mortality rate of 11.4/100 PYFU (95% CI 10.0-13.1). Almost half of those (48.8%) died of TB. The proportion of all

TB-related deaths was highest in the first 6 (n =49/71; 69%; P <0.0001) and 6-24 (n =33/58; 56.9%; P <0.0001) months of follow-up, compared deaths beyond 24 months (n =23/85; 26.7%).
CONCLUSION: TB recurrence and TB-related mortality rates in PWH in Eastern Europe are still concerningly high and continue to be a clinical and public health challenge.

DOI: 10.1097/QAD.0000000000003670
PMID: 37503671 [Indexed for MEDLINE]

34. Incidence and Patterns of Drug Resistance in Patients with Spinal Tuberculosis: a Prospective, Single-Center Study from a Tuberculosis-Endemic Country.

Indian J Orthop. 2023 Sep 7;57(11):1833-1841. doi: 10.1007/s43465-023-00986-4. eCollection 2023 Nov.

Yadav M(1), Jain AK(1), Singhal R(2), Chadha M(1), Arora VK(3), Bhargava A(1).

BACKGROUND: There is paucity of data on incidence and pattern of drug resistance in spinal TB. This prospective observational study was conducted to document the incidence and drug-resistance pattern among primary and presumptive resistant cases.
METHODS: 59 consecutive cases diagnosed clinico-radiologically (imaging) were grouped into Group A (n = 51, primary cases) and Group B (n = 8, presumptive resistant cases) based on pre-defined criteria (INDEX-TB guidelines). Tissue samples obtained percutaneously (37.29%, 22/59) and on surgery (62.71%, 37/59) were subjected to genotypic DST (CBNAAT, LPA) and phenotypic DST (BACTEC MGIT 960 culture and sensitivity using fixed critical concentration of drugs).
RESULTS: Etiological diagnosis was ascertained in all. 13/51 (25.49%) in Group A, while 3/8 (37.5%) in Group B and 16/59 (27.12%) overall demonstrated drug resistance. 12/16 (75%) had no prior history of ATT intake. 4 demonstrated INH (Isoniazid) mono-resistance. 12 polydrug resistance demonstrated: 5MDR, 3pre-XDR, while RIF + FQ (fluoroquinolones), FQ + Lz (linezolid), only SLID (second-line injectable drugs), and only FQ resistance observed in 1 case each. Isolated RIF (Rifampicin) resistance and XDR pattern were not observed. Overall frequency of RIF resistance was 16.4% (9/55) and INH was 25% (12/48) with low-(n-2) and high-level INH resistance (n-10). Among second-line drugs, FQ resistance was more than SLID resistance and within FQ, levofloxacin resistance was more frequent than moxifloxacin. MGIT demonstrated positive growth in 16/59 samples, out of which 1 sample was positive for nontuberculous mycobacteria (M. chelonae) but on genotypic testing demonstrated MTB resistant to RIF and FQ.
CONCLUSION: This is the first report on incidence and drug-resistant pattern in

culture-positive/negative cases. High (25.49%) primary drug resistance is worrisome. This being the first study in spinal TB cases which document prevalent drug-resistant pattern as evaluated for consecutive culture-positive/negative cases. The tissue obtained must be submitted for AFB culture and molecular tests to ascertain drug resistance in culture-positive/negative cases. However, in the presence of insufficient tissue sample histology and CBNAAT can ascertain etiological diagnosis in 100% cases. INH resistance is more than RIF with isolated RIF resistance unreported.

DOI: 10.1007/s43465-023-00986-4
PMCID: PMC10593722
PMID: 37881297

Conflict of interest statement: Conflict of interestOn behalf of all authors, the corresponding author states that there is no conflict of interest.

35. How has the municipal availability of the GeneXpert®MTB/RIF system affected the detection of drug-resistant tuberculosis in Brazil?

Trop Med Int Health. 2023 Nov 2. doi: 10.1111/tmi.13945. Online ahead of print.

Aguilar-Jiménez JR(1)(2), Pelissari DM(3), Diaz-Quijano FA(4).

OBJECTIVE: To evaluate the association between the availability of GeneXpert®MTB/RIF in municipalities and the proportion of people who have access to this diagnostic technology for tuberculosis (TB), as well as the resistance detected by the surveillance system in Brazil.
METHODS: We analysed 4998 Brazilian municipalities that reported 432,937 new TB cases between 2015 and 2020. We compared municipalities with and without the availability of GeneXpert®MTB/RIF regarding the effective access to GeneXpert®MTB/RIF diagnosis and the prevalence of detected resistance.
RESULTS: Municipalities with at least one GeneXpert®MTB/RIF system had three times (95% CI 2.9-3.0) the access to diagnostic tests and 80.4% (95% CI 70.6%-90.2%) higher detection of resistance, compared with municipalities without this technology. We estimated that there have been 1890 cases of undetected resistance during this period in the country.
CONCLUSIONS: The availability of GeneXpert®MTB/RIF system in the municipality increased the sensitivity of the surveillance for detecting TB resistance.

PUBLIC HEALTH IMPLICATIONS: It is a priority to strengthen laboratory networks and narrow the gap in access to rapid diagnosis in remote areas to improve the detection and control of drug-resistant tuberculosis.

DOI: 10.1111/tmi.13945
PMID: 37919228

36. A descriptive study on isoniazid resistance-associated mutations, clustering and treatment outcomes of drug-resistant tuberculosis in a high burden country.

Eur J Clin Microbiol Infect Dis. 2023 Nov 9. doi: 10.1007/s10096-023-04693-8. Online ahead of print.

Pinhata JMW(1), Ferrazoli L(2), Mendes FF(2), Gonçalves MG(2), Rabello MCDS(3), Ghisi KT(2), Simonsen V(2), Cavalin RF(4), Lindoso AABP(4), de Oliveira RS(2).

PURPOSE: To describe katG and inhA mutations, clinical characteristics, treatment outcomes and clustering of drug-resistant tuberculosis (TB) in the State of São Paulo, southeast Brazil.
METHODS: Mycobacterium tuberculosis isolates from patients diagnosed with drug-resistant TB were screened for mutations in katG and inhA genes by line probe assay and Sanger sequencing, and typed by IS6110-restriction fragment-length polymorphism for clustering assessment. Clinical, epidemiological and demographic data were obtained from surveillance information systems for TB.
RESULTS: Among the 298 isolates studied, 127 (42.6%) were isoniazid-monoresistant, 36 (12.1%) polydrug-resistant, 93 (31.2%) MDR, 16 (5.4%) pre-extensively drug-resistant (pre-XDR), 9 (3%) extensively drug-resistant (XDR) and 17 (5.7%) susceptible after isoniazid retesting. The frequency of katG 315 mutations alone was higher in MDR isolates, while inhA promoter mutations alone were more common in isoniazid-monoresistant isolates. Twenty-six isolates phenotypically resistant to isoniazid had no mutations either in katG or inhA genes. The isolates with inhA mutations were found more frequently in clusters (75%) when compared to the isolates with katG 315 mutations (59.8%, p = 0.04). In our population, being 35-64 years old, presenting MDR-, pre-XDR- or XDR-TB and being a retreatment case were associated with unfavourable TB treatment outcomes.
CONCLUSION: We found that katG and inhA mutations were not equally distributed between isoniazid-monoresistant and MDR isolates. In our population, clustering was higher for isolates with inhA mutations. Finally, unfavourable TB outcomes were associated with specific factors.

DOI: 10.1007/s10096-023-04693-8
PMID: 37943394

37. Whole genome sequencing of drug resistant Mycobacterium tuberculosis isolates in Victoria, Australia.

Int J Infect Dis. 2023 Nov 13:S1201-9712(23)00771-3. doi: 10.1016/j.ijid.2023.11.010. Online ahead of print.

Dorji T(1), Horan K(2), Sherry NL(3), Tay EL(4), Globan M(5), Viberg L(5), Bond K(6), Denholm JT(7), Howden BP(8), Andersson P(3).

OBJECTIVES: Whole genome sequencing (WGS) can identify clusters, transmission patterns and drug resistance mutations. This is important in low-burden settings such as Australia, as it can assist in efficient contact tracing and surveillance.
METHODS: We conducted a retrospective cohort study using WGS from 155 genomically defined drug-resistant M. tuberculosis (DR-TB) isolates collected between 2018-2021 in Victoria, Australia. Bioinformatic analysis was performed to identify resistance conferring mutations, lineages, clusters and understand how local sequences compared with international context.
RESULTS: Of the 155 sequences, 42% was identified as lineage 2 and 35% as lineage 1; 65.8% (102/155) were isoniazid mono-resistant, 8.4% were multi-drug resistant TB and 5.8% were pre-extensively drug-resistant / extensively drug-resistant TB. The most common mutations were observed in katG and fabG1 gene especially at Ser315Thr and fabG1 -15 C>T for first line drugs. Ser450Leu was the most frequent mutation in rpoB gene. Phylogenetic analysis confirmed that Victorian DR-TB were associated with importation events. There was little evidence of local transmission with only five isolate pairs.
CONCLUSION: Isoniazid resistant TB is the commonest DR-TB in Victoria, and the mutation profile is similar to global circulating DR-TB. Most cases are diagnosed among migrants with limited transmission. This study highlights the value of WGS in identification of clusters and resistance conferring mutations. This information is crucial in supporting disease mitigation and treatment strategies.

DOI: 10.1016/j.ijid.2023.11.010
PMID: 37967715

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

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

Eur Respir J. 2023 Nov 9:2300639. doi: 10.1183/13993003.00639-2023. Online ahead of print.

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

DOI: 10.1183/13993003.00639-2023
PMID: 37945030

39. Investigation of genomic mutations and their association with phenotypic resistance to new and repurposed drugs in Mycobacterium tuberculosis complex clinical isolates.

J Antimicrob Chemother. 2023 Nov 6;78(11):2637-2644. doi: 10.1093/jac/dkad252.

Mok S(1)(2), Roycroft E(1)(2), Flanagan PR(1)(2), Wagener J(1)(2), Fitzgibbon MM(1)(2).

BACKGROUND: WGS has the potential to detect resistance-associated mutations and guide treatment of MDR TB. However, the knowledge base to confidently interpret mutations associated with the new and repurposed drugs is sparse, and phenotypic drug susceptibility testing is required to detect resistance.
METHODS: We screened 900 Mycobacterium tuberculosis complex genomes from Ireland, a low TB incidence country, for mutations in 13 candidate genes and assessed their association with phenotypic resistance to bedaquiline, clofazimine, linezolid, delamanid and pretomanid.
RESULTS: We identified a large diversity of mutations in the candidate genes of 195 clinical isolates, with very few isolates associated with phenotypic resistance to bedaquiline (n = 4), delamanid (n = 4) and pretomanid (n = 2). We identified bedaquiline resistance among two drug-susceptible TB isolates that harboured mutations in Rv0678. Bedaquiline resistance was also identified in two MDR-TB isolates harbouring Met146Thr in Rv0678, which dated back to 2007, prior to the introduction of bedaquiline. High-level delamanid resistance was observed in two isolates with deletions in ddn, which were also resistant to pretomanid. Delamanid resistance was detected in two further isolates that harboured mutations in fbiA, but did not show cross-resistance to pretomanid. All isolates were susceptible to linezolid and clofazimine, and no mutations found were

associated with resistance.
CONCLUSIONS: More studies that correlate genotypic and phenotypic drug susceptibility data are needed to increase the knowledge base of mutations associated with resistance, in particular for pretomanid. Overall, this study contributes to the development of future mutation catalogues for M. tuberculosis complex isolates.

DOI: 10.1093/jac/dkad252
PMID: 37740935 [Indexed for MEDLINE]

40. [Study on the resistance of rifampicin-resistant Mycobacterium tuberculosis to anti-tuberculosis drugs in group A].

Zhonghua Jie He He Hu Xi Za Zhi. 2023 Nov 12;46(11):1110-1117. doi: 10.3760/cma.j.cn112147-20230804-00046.

Dai XW(1), Li CY(1), Wang NH(1), Chen SS(1), Tian LL(1), Zhao YF(1), Tao LY(1), Yang XY(1), Ding BC(1), He XX(1).

Objective: To summarize the resistance of rifampicin-resistant Mycobacterium tuberculosis to anti-tuberculosis drugs in group A. Methods: In the retrospective study, a total of 1 226 clinical isolates from suspected multidrug-resistant pulmonary tuberculosis patients in Beijing TB control system from 2016 to 2021 were identified as Mycobacterium tuberculosis (MTB) strains by MPB64 antigen detection test. Rifampicin-resistant tuberculosis (RR-TB) strains were screened by the phenotypic drug susceptibility using the proportion method. The drug susceptibilities of Levofloxacin(LFX), Moxifloxacin(MFX), Bedaquiline(BDQ) and Linezolid(LZD)were detected by the phenotypic drug susceptibility with microplate method. The drug resistance rate, drug resistance level and minimum inhibitory concentration (MIC) distribution of four anti-tuberculosis drugs in group A were analyzed. We calculated the demographic distribution of RR-TB, multidrug-resistant tuberculosis(MDR-TB), pre-extensively drug resistant tuberculosis (pre-XDR-TB), extensively drug resistant tuberculosis (XDR-TB) patients and the cross resistance of LFX and MFX, then summarized the drug-resistance spectrum of BDQ-resistant and LZD-resistant strains and the treatment outcome of RR-TB patients. Measurement data were expressed as rate or composition ratio,$\chi 2$ test was used between and within groups, and $P<0.05$ was considered statistically significant. Results: Among the 1 226 suspected multidrug-resistant pulmonary tuberculosis patients, the detection rates of RR/MDR/pre-XDR/XDR-TB patients were 20.8%(255/1 226),

15.2%(186/1 226), 5.7%(70/1 226), 0.5%(6/1 226), respectively. There were statistically significant differences in the distribution of patients with the four types of drug resistance in terms of age and treatment history (χ2=14.95, P=0.020;χ2=15.91, P=0.001). The drug resistance rates of LFX, MFX, BDQ and LZD in RR-TB patients were 27.5% (70/255), 27.5% (70/255), 0.4% (1/255) and 2.4% (6/255), respectively. The MICs of LFX, MFX and LZD-susceptible MTB were mainly at 0.25 mg/L, and the MIC of BDQ-susceptible MTB was mainly concentrated at 0.03 mg/L. 25.1% (64/255) of the RR MTB were resistant to both LFX and MFX, and 6 strains were resistant to LFX or MFX, showing incomplete two-way cross resistance. One BDQ-resistant strain and six LZD-resistant strains were detected. The treatment success rate of RR-TB patients was 74.4% (151/203), and there were statistically significant differences in treatment outcomes between resistant and sensitive patients on the LFX-containing treatment regimen (Fisher's exact test, P=0.012). Conclusions: The prevalence of fluoroquinolones (LFX and MFX) resistance in rifampicin-resistant MTB is very serious. LFX and MFX show incomplete bidirectional cross-resistance. BDQ and LZD have the most promising future in the treatment of MDR-TB. Improve drug-resistance testing will help to further improve the success rate of treatment.

DOI: 10.3760/cma.j.cn112147-20230804-00046
PMID: 37914422 [Indexed for MEDLINE]

41. [Treatment of MDR, pre-XDR, XDR and rifampicin resistant tuberculosis or in case of intolerance to at least rifampicin in Austria, Germany and Switzerland - Amendment dated 19.09.2023 to the Sk2-Guideline: Tuberculosis in adulthood of the German Central Committee against Tuberculosis (DZK) on behalf of the German Respiratory Society (DGP)].

Pneumologie. 2023 Nov 6. doi: 10.1055/a-2182-1609. Online ahead of print.

Otto-Knapp R(1), Bauer T(1)(2), Brinkmann F(3), Feiterna-Sperling C(4), Friesen I(5), Geerdes-Fenge H(6), Hartmann P(7), Häcker B(1), Hauer B(8), Haas W(8), Heyckendorf J(9), Kuhns M(5), Lange C(10)(11)(12)(13), Maurer FP(14), Nienhaus A(15), Priwitzer M(16), Richter E(17), Salzer HJF(18)(19)(20), Schoch O(21), Schönfeld N(2), Schaberg T(1).

In December 2022, based on the assessment of new evidence, the World Health Organization (WHO) updated its guidelines for the treatment of drug-resistant tuberculosis (TB). The evaluation of both, these recommendations, and the latest study data, makes it necessary to update the existing guidelines on the treatment of at least rifampicin-resistant tuberculosis for the German-speaking region, hereby replacing the respective chapters. A shortened MDR-TB treatment of at least 6 month using the fixed and non-modifiable drug combination of bedaquiline, pretomanid, linezolid, and moxifloxacin (BPaLM) is now also

recommended for Germany, Austria, and Switzerland under certain conditions. This recommendation applies to TB cases with proven rifampicin resistance, including rifampicin monoresistance. For treatment of pre-extensively drug resistant TB (pre-XDR-TB), an individualized treatment for 18 months adjusted to resistance data continues to be the primary recommendation. The non-modifiable drug combination of bedaquiline, pretomanid, and linezolid (BPaL) may be used alternatively in pre-XDR TB if all prerequisites are met. The necessary prerequisites for the use of BPaLM and BPaL are presented in this amendment to the S2k guideline for 'Tuberculosis in adulthood'.

DOI: 10.1055/a-2182-1609
PMID: 37931778

Conflict of interest statement: Informationen zu Interessenkonflikten finden Sie auf den Seiten der AWMF (http://www.awmf.org/leitlinien/awmf-regelwerk.html).

42. Cost of digital technologies and family-observed DOT for a shorter MDR-TB regimen: a modelling study in Ethiopia, India and Uganda.

BMC Health Serv Res. 2023 Nov 18;23(1):1275. doi: 10.1186/s12913-023-10295-z.

Rosu L(1), Madan J(2), Bronson G(3), Nidoi J(4), Tefera MG(5), Malaisamy M(6), Squire BS(7), Worrall E(8).

BACKGROUND: In 2017, the WHO recommended the use of digital technologies, such as medication monitors and video observed treatment (VOT), for directly observed treatment (DOT) of drug-susceptible TB. The WHO's 2020 guidelines extended these recommendations to multidrug-resistant tuberculosis (MDR-TB), based on low evidence. The impact of COVID on health systems and patients underscored the need to use digital technologies in the management of MDR-TB.
METHODS: A decision-tree model was developed to explore the costs of several potential DOT alternatives: VOT, 99DOTS (Directly-observed Treatment, Short-course) and family-observed DOT. Assuming a 9-month, all-oral regimen (as evaluated within the STREAM trial), we constructed base-case cost models for the standard-of-care DOTs in Ethiopia, India, and Uganda, as well as for the three alternative DOT approaches. The models were populated with STREAM Stage 2 clinical trial outcome and cost data, supplemented with market prices data for the digital DOT strategies. Sensitivity analyses were conducted on key parameters.
RESULTS: Modelling suggested that the standard-of-care DOT approach is the most expensive DOT strategy from a societal perspective in all three countries evaluated (Ethiopia, India, Uganda), with considerable direct- and

indirect-costs incurred by patients. The second most expensive DOT approach is VOT, with high health-system costs, largely caused by up-front technology expenditure. Each of VOT, 99DOTS and family-observed DOT would reduce by more than 90% patients' direct and indirect costs compared to standard of care DOT. Results were robust to the sensitivity analyses.
CONCLUSIONS: While data on the costs and efficacy of alternative DOT approaches in the context of shorter MDR-TB treatment is limited, our modelling suggests alternative DOT approaches can significantly reduce patient costs in all three countries. Health system costs are higher for VOT and lower for 99DOTS and family-observed therapy when compared to standard of care DOT, as low smartphone penetration and internet availability requires the VOT health system to fund the cost of making them available to patients.

DOI: 10.1186/s12913-023-10295-z
PMCID: PMC10657602
PMID: 37980524

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

43. Efficacy and safety of the all-oral bedaquiline-containing regimen as treatment for pediatric multidrug/rifampicin-resistant tuberculosis: a multicenter, retrospective, cohort study.

Expert Rev Anti Infect Ther. 2023 Nov 20. doi: 10.1080/14787210.2023.2285917. Online ahead of print.

Sun WW(1), Yang M(2), Chen XH(3), Fan LC(4), Wu HY(4), Zhang SJ(1), Chen Y(4), Fan L(1).

OBJECTIVE: The study aimed to observe the efficacy and safety of an all-oral bedaquiline (BDQ)-containing regimen for pediatric multidrug/rifampicin-resistant tuberculosis (MDR/RR-TB) through a multicenter, retrospective study in China.
METHODS: In the study, pediatric patients receiving all-oral BDQ-containing regimen (BDQ group) with clinical matched control group were included, the control group received an injection-containing regimen. The treatment outcomes and the incidence of adverse events (AEs) were compared and analyzed.
RESULTS: 79 pediatric patients were enrolled, including 37 cases in BDQ group and 42 cases in the control group, the median age was 12 {8-16} and 11 {9-15} in both groups respectively. Favorable treatment outcome and cure rate in BDQ group were significantly higher than those in control group (100%vs 83.3%, p 0.03; 94.6%vs 63.3%, p 0.00). Median time of sputum culture conversion in BDQ group

was significantly shorter than that in the control group (4 weeks vs 8 weeks, p 0.00). The incidence of AEs in the BDQ group was significantly less than that in the control group (48.6% vs 71.4%, p 0.03). No AEs leading to treatment discontinuation of BDQ occurred.
CONCLUSIONS: The all-oral BDQ-containing regimens may be effective and safe in the Chinese pediatric population.

DOI: 10.1080/14787210.2023.2285917
PMID: 37982155

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

ACS Infect Dis. 2023 Nov 3. doi: 10.1021/acsinfecdis.3c00317. Online ahead of print.

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

Pseudomonas aeruginosa (PA) is a Gram-negative, biofilm-forming bacterium and an opportunistic pathogen. The growing drug resistance of PA is a serious threat that necessitates the discovery of novel antibiotics, ideally with previously underexplored mechanisms of action. Due to their central role in cell metabolism, bacterial bioenergetic processes are of increasing interest as drug targets, especially with the success of the ATP synthase inhibitor bedaquiline to treat drug-resistant tuberculosis. Like Mycobacterium tuberculosis, PA requires F1Fo ATP synthase for growth, even under anaerobic conditions, making the PA ATP synthase an ideal drug target for the treatment of drug-resistant infection. In previous work, we conducted an initial screen for quinoline compounds that inhibit ATP synthesis activity in PA. In the present study, we report additional quinoline derivatives, including one with increased potency against PA ATP synthase in vitro and antibacterial activity against drug-resistant PA. Moreover, by expressing the PA ATP synthase in Escherichia coli, we show that mutations in the H+ binding site on the membrane-embedded rotor ring alter inhibition by the reported quinoline compounds. Identification of a potent inhibitor and its probable binding site on ATP synthase enables further development of promising quinoline derivatives into a viable treatment for drug-resistant PA infection.

DOI: 10.1021/acsinfecdis.3c00317
PMID: 37922420

45. Expanding the squaramide library as mycobacterial ATP synthase inhibitors: Innovative synthetic pathway and biological evaluation.

Bioorg Med Chem. 2023 Nov 15;95:117504. doi: 10.1016/j.bmc.2023.117504. Epub 2023 Oct 18.

Chasák J(1), Oorts L(2), Dak M(1), Šlachtová V(1), Bazgier V(3), Berka K(3), De Vooght L(2), Smiejkowska N(2), Calster KV(2), Van Moll L(2), Cappoen D(2), Cos P(2), Brulíková L(4).

Mycobacterial ATP synthase is a validated therapeutic target for combating drug-resistant tuberculosis. Inhibition of this enzyme has been featured as an efficient strategy for the development of new antimycobacterial agents against drug-resistant pathogens. In this study, we synthesised and explored two distinct series of squaric acid analogues designed to inhibit mycobacterial ATP synthase. Among the extensive array of compounds investigated, members of the phenyl-substituted sub-library emerged as primary hits. To gain deeper insights into their mechanisms of action, we conducted advanced biological studies, focusing on the compounds displaying a direct binding of a nitrogen heteroatom to the phenyl ring, resulting in the highest potency. Our investigations into spontaneous mutants led to the validation of a single point mutation within the atpB gene (Rv1304), responsible for encoding the ATP synthase subunit a. This genetic alteration sheds light on the molecular basis of resistance to squaramides. Furthermore, we explored the possibility of synergy between squaramides and the reference drug clofazimine using a checkerboard assay, highlighting the promising avenue for enhancing the effectiveness of existing treatments through combined therapeutic approaches. This study contributes to the expansion of investigating squaramides as promising drug candidates in the ongoing battle against drug-resistant tuberculosis.

DOI: 10.1016/j.bmc.2023.117504
PMID: 37871508 [Indexed for MEDLINE]

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

46. [Expert consensus on off-label use of antituberculosis drugs (2023 Update)].

Zhonghua Jie He He Hu Xi Za Zhi. 2023 Nov 12;46(11):1085-1102. doi: 10.3760/cma.j.cn112147-20230809-00062.

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

Chinese Society for Tuberculosis, Chinese Medical Association.

In 2018, Chinese Society of Tuberculosis, Chinese Medical Association organized and wrote the Expert consensus on off-label use of antituberculosis drugs, which covered more comprehensively the contents related to off-label use of antituberculosis drugs, and was the basis for clinical workers to exceed the drug instructions for the use of antituberculosis treatment in irreplaceable cases, and was also a good regulation for off-label use, which had a great guiding effect on clinical work. In the last four years, with the reported national and international research results, the anti-tuberculosis treatment drugs have been adjusted and there are more new advances in the use of some drugs. For this reason, Chinese Society for Tuberculosis, Chinese Medical Association has updated the expert consensus on off-label use of antituberculosis drugs. This consensus included isoniazid, rifamycins (rifampicin, rifapentine), fluoroquinolones (levofloxacin, moxifloxacin), linezolid, clofazimine, bedaquiline, delamanid, aminoglycosides (streptomycin, amikacin), and β-lactam antibacterial (imipenem/cilastatin, meropenem), and a total of 13 drugs in 9 categories were reviewed for off-label use, overdose, route of administration and patient populations. The GRADE evidence classification method was used to conduct a systematic evaluation of evidence quality and recommended strength. The revised consensus provides a reference for tuberculosis prevention and control workers in China for standardized drug use and rationalized treatment, and therefore for improved effectiveness and better patient benefits.

DOI: 10.3760/cma.j.cn112147-20230809-00062
PMID: 37914420 [Indexed for MEDLINE]

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

Antimicrob Agents Chemother. 2023 Nov 15:e0078923. doi: 10.1128/aac.00789-23. Online ahead of print.

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

Contezolid is a new oxazolidinone with in vitro and in vivo activity against Mycobacterium tuberculosis comparable to that of linezolid. Pre-clinical and clinical safety studies suggest it may be less toxic than linezolid, making contezolid a potential candidate to replace linezolid in the treatment of

drug-resistant tuberculosis. We evaluated the dose-ranging activity of contezolid, alone and in combination with bedaquiline and pretomanid, and compared it with linezolid at similar doses, in an established BALB/c mouse model of tuberculosis. Contezolid had an MIC of 1 µg/mL, similar to linezolid, and exhibited similar bactericidal activity in mice. Contezolid-resistant mutants selected in vitro had 32- to 64-fold increases in contezolid MIC and harbored mutations in the mce3R gene. These mutants did not display cross-resistance to linezolid. Our results indicate that contezolid has the potential to replace linezolid in regimens containing bedaquiline and pretomanid and likely other regimens.

DOI: 10.1128/aac.00789-23
PMID: 37966090