PubMed Open Access

1.Treatment outcomes of extensively drug-resistant tuberculosis in Europe: a retrospective cohort study.

Lancet Reg Health Eur. 2025 Jul 15;56:101380. doi: 10.1016/j.lanepe.2025.101380. eCollection 2025 Sep.

Kherabi Y(1)(2), Skouvig Pedersen O(3)(4), Lange C(5)(6)(7)(8), Bénézit F(9), Chesov D(5)(6)(10)(11), Codecasa LR(12), Dudnyk A(13)(14), Kiria N(15), Konstantynovska O(16)(17)(18), Marigot-Outtandy D(19), Panciu TC(20), Poignon C(21)(22), Sasi S(23), Schaub D(5)(6)(7), Solodovnikova V(24), Vasiliauskaitė L(25)(26), Yeghiazaryan L(27), Günther G(28)(29), Guglielmetti L(30); TBnet/ESGMYC XDR-TB Study Group.

Collaborators: Aubry A, Vasiliu A, Dudnyk A, McLaughlin AM, Lange C, Poignon C, Schaub D, Cirillo D, Podlekareva D, Marigot-Outtandy D, Chesov D, Davidavičienė E, Bénézit F, Fumagalli G, Troia G, Günther G, Motta I, Jonsson J, Robert J, Eimer J, Vasiliauskaitė L, Kuska L, Guglielmetti L, Codecasa LR, Yeghiazaryan L, Skowroński M, Fitzgibbon M, Revest M, Kiria N, Veziris N, Pedersen OS, Konstantynovska O, Opota O, Viiklepp P, Coriu R, Tunesi S, Sasi S, Skogmar S, Bjerrum S, Togonidze T, Panciu TC, Lillebaek T, Pourcher V, Solodovnikova V, Le VB, Kherabi Y.

Author information:
(1)Infectious and Tropical Diseases Department, Bichat-Claude Bernard Hospital, Assistance Publique-Hôpitaux de Paris, Université Paris Cité, Paris, France.
(2)Université Paris Cité, Inserm, IAME, Paris, France.
(3)Department of Respiratory Medicine and Allergy, Aarhus University Hospital, Aarhus, Denmark.
(4)Department of Clinical Medicine, Aarhus University, Aarhus, Denmark.
(5)Division of Clinical Infectious Diseases, Research Center Borstel, Borstel, Germany.
(6)German Center for Infection Research (DZIF), Partner Site Hamburg-Lübeck-Borstel-Riems, Borstel, Germany.
(7)Respiratory Medicine and International Health, University of Lübeck, Lübeck, Germany.
(8)Baylor College of Medicine and Texas Children Hospital, Global TB Program, Houston, TX, USA.
(9)Infectious Disease and Intensive Care Unit, Pontchaillou University Hospital, Rennes, France.
(10)Nicolae Testemitanu State University of Medicine and Pharmacy, Chisinau, Republic of Moldova.
(11)Chiril Draganiuc Pneumology Institute, Chisinau, Republic of Moldova.

(12)Regional TB Reference Centre, Instituto Villa Marelli, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy.
(13)Department of Tuberculosis, Clinical Immunology and Allergy, National Pirogov Memorial Medical University, Vinnytsia, Ukraine.
(14)Institut d'Investigació Germans Trias i Pujol (IGTP), Barcelona, Spain.
(15)National Center for Tuberculosis and Lung Diseases, Tbilisi, Georgia.
(16)Department of Infectious Diseases and Clinical Immunology, V.N. Karazin Kharkiv National University, Kharkiv, Ukraine.
(17)"Regional Phtisiopulmonological Center" of the Kharkiv Regional Council, Communal Non-commercial Enterprise, Kharkiv, Ukraine.
(18)Department of Infectious Disease, Imperial College London, London, UK.
(19)Sanatorium, Centre Hospitalier de Bligny, Briis-sous-Forges, France.
(20)Marius Nasta Institute of Pneumology Bucharest, Bucharest, Romania.
(21)Sorbonne-Université, INSERM, CNRS, Centre d'Immunologie et de Maladies Infectieuses, CIMI, Paris, France.
(22)Assistance Publique Hôpitaux de Paris, Groupe Hospitalier Universitaire Sorbonne Université, Hôpital Pitié-Salpêtrière, Centre National de Référence des Mycobactéries et de la Résistance des Mycobactéries aux Antituberculeux, Paris, France.
(23)Department of Microbiology and Molecular Diagnostics, Laboratory, North Estonia Medical Centre, Tallinn, Estonia.
(24)TBnet, Bad Oldesloe, Germany.
(25)Department of Physiology, Biochemistry, Microbiology and Laboratory Medicine, Institute of Biomedical Sciences, Faculty of Medicine, Vilnius University, Vilnius, Lithuania.
(26)Centre of Laboratory Medicine, Laboratory of Infectious Diseases and Tuberculosis, Vilnius University Hospital Santaros Klinikos, Vilnius, Lithuania.
(27)National Center of Pulmonology, Abovyan, Republic of Armenia.
(28)Department of Pulmonary Medicine, Allergology and Clinical Immunology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland.
(29)Department of Medical Sciences, School of Medicine, University of Namibia, Windhoek, Namibia.
(30)Department of Infectious, Tropical Diseases and Microbiology, IRCCS Sacro Cuore Don Calabria Hospital, Negrar di Valpolicella, Verona, Italy.

BACKGROUND: In 2021, World Health Organization revised of definition of extensive drug-resistant tuberculosis. We aimed to determine treatment outcomes of individuals affected by extensively drug-resistant tuberculosis in Europe.
METHODS: This observational, retrospective cohort study included patients diagnosed with extensively drug-resistant tuberculosis in the World Health Organization European Region from 2017 to 2023. Participating centres collected consecutive, detailed individual data for extensively drug-resistant tuberculosis patients. Data were analysed with meta- and regression methods, accounting for between-country heterogeneity.

FINDINGS: Among 11,003 patients with multidrug-resistant/rifampicin-resistant tuberculosis, 188 (1·7%) from 16 countries had extensively drug-resistant tuberculosis. Of these, 48·4% harboured strains with resistance to bedaquiline (n = 91/188), 34·0% to linezolid (n = 64/188), and 17·6% to both (n = 33/188). The individual composition of anti-tuberculosis regimens was highly variable, with 151 different drug combinations. Among the 156/188 (83·0%) patients with available treatment outcomes, the pooled percentage of successful outcomes was 40·2% (95% confidence interval [95% CI] 28·4%-53·2%). In patients with unsuccessful treatment outcomes (101/156), most experienced treatment failure (n = 57/156 [pooled proportion 37·1%], 95% CI: 26·1%-49·7%) or death (n = 30/156 [pooled proportion 21·3%], 95% CI: 15·7%-28·2%). After adjustment for disease severity, each additional likely effective drug decreased the odds of unsuccessful outcomes (adjusted odds ratio: 0·65, 95% CI: 0·45-0·96) (p = 0·026), whereas being treated in an upper-middle-income country increased the odds of unsuccessful outcomes compared with being treated in a high-income country (adjusted odds ratio: 13·7, 95% CI: 3·7-50·2) (p < 0·001). Compared with other levels of drug resistance, treatment outcomes were significantly worse for extensively drug-resistant tuberculosis.
INTERPRETATION: Only four out of ten patients affected by extensively drug-resistant tuberculosis achieved successful treatment outcomes. These findings highlight the need for adequate, individualised treatment regimens and optimised drug susceptibility testing.
FUNDING: None.

DOI: 10.1016/j.lanepe.2025.101380
PMCID: PMC12281379
PMID: 40697337

Conflict of interest statement: LG is co-Principal Investigator of two MSF-sponsored Phase III randomised controlled clinical trials (endTB & endTB-Q) testing new shorter regimens for MDR/RR-TB. Both trials are mainly funded by Unitaid. LG is PI of a Phase III clinical trial (FAST-MDR) which is funded by the French National Hospital Program for Clinical Research (PHRC) and by a pro-bono donation by Viatris. CL is the clinical lead of the UNITE4TB consortium which conducts clinical tuberculosis trials in Phase IIa-c. CL received honoraria for speaking at symposia sponsored by Astra Zeneca, Gilead, GSK, Insmed, medUpdate, MedUpdateEurope, and Pfizer outside of the scope of this study. LRC received honoraria for speaking at symposia sponsored by Viatris and participated in an advisory board for Cepheid outside of the scope of this study. All other authors declare no competing interests.

2. Genomic epidemiology analysis of extremely drug-resistant tuberculosis in Shanghai, China.

Emerg Microbes Infect. 2025 Dec;14(1):2521842. doi: 10.1080/22221751.2025.2521842. Epub 2025 Jul 4.

Lu X(1), Jiang Y(2), Liu Y(1), Chen J(1), Lao Y(1), Li J(2), Zhang Y(2), Li N(1), Wang L(2), Yu C(2), Ye Q(1), Wei W(1), Deng J(1), Shen X(2), Yang C(1).

Author information:
(1)School of Public Health (Shenzhen), Shenzhen Key Laboratory of Pathogenic Microbes and Biosafety, Shenzhen Campus of Sun Yat-sen University, Sun Yat-sen University, Guangdong, People's Republic of China.
(2)Division of TB and HIV/AIDS Prevention, Shanghai Municipal Center for Disease Control and Prevention, Shanghai, People's Republic of China.

Tuberculosis (TB), particularly extremely drug-resistant TB (EDR-TB), remains a significant public health concern worldwide. Understanding the transmission patterns and epidemiological characteristics of EDR-TB is vital for effective disease control. Between 1 January 2006 and 31 December 2018, we collected clinical M. tuberculosis strains in Shanghai, with whole-genome sequencing performed on 58 identified clinical EDR-TB strains. We analyzed EDR-related genetic mutations, conducted phylogenetic analyses, and examined bacterial and epidemiological factors that influence their transmission. Among these 58 EDR patients, 43.1% (25/58) were aged 45-64 years, with a median age of 51 years (interquartile range, IQR, 29-59 years). About two-thirds of the EDR-TB patients were residents. We observed a clustering rate of 44.8% (26/58) among EDR strains. Logistic regression analysis indicated a higher risk of recent EDR-TB transmission among the strains with the drug-resistant compensatory mutations. The primary mode of EDR-TB transmission in the study setting was recent, direct person-to-person spread of drug-resistant strains, as evidenced by high clustering rates and the presence of identical resistance mutations among clustered cases.

DOI: 10.1080/22221751.2025.2521842
PMCID: PMC12231322
PMID: 40548454 [Indexed for MEDLINE]

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

3.Performance of the low-cost phenotypic thin-layer agar MDR/XDR-TB Colour Test (first generation, 1G, Color Plate Test) for identifying drug-resistant Mycobacterium tuberculosis isolates in a resource-limited setting.

Res Sq [Preprint]. 2025 Jun 27:rs.3.rs-6697928. doi: 10.21203/rs.3.rs-6697928/v1.

Mebrat B, Garcia JI, Woldeamanuel Y, Adane K, Hicks A, Tilahun M, Neway S, Oluma L, Atnafu A, Gelfond J, Evans CA, Torrelles JB, Wang SH, Wassie L.

Background: The accessible, easy to use and timely, diagnosis of tuberculosis (TB) drug-susceptibility, including multi-drug resistant (MDR-) TB and extensively-drug resistant (XDR-)TB is often challenging, particularly in resource-constrained settings. We therefore evaluated the phenotypic thin-layer agar based MDR/XDR-TB Colour Test, which is also referred to as the "First Generation (1G) Color Plate Test (TB-CX)" performance for detecting resistance of Mycobacterium tuberculosis (Mtb) isolates to selected anti-TB drugs versus other tests routinely used in our setting. Methods: A cross-sectional study was conducted on Mtb clinical isolates stored at the Armauer Hansen Research Institute TB laboratory in Addis Ababa, Ethiopia. Drug-susceptibility testing was performed on 78 Mtb isolates for isoniazid, rifampicin, and moxifloxacin using the Colour Test and the Indirect Proportional Method (IPM) "in house" assay. Isoniazid and rifampicin were also evaluated by the Mycobacterial Growth Indicator Tube (MGIT) commercially available assay. Test accuracy was calculated as % agreement with 95% confidence intervals (95%CI). Results: The median (range) times in days determining Mtb resistance or susceptibility for the Colour Test, IPM and MGIT assays were of 9 (5-18), 15 (13-18) and 18 (14-21) days, respectively. The Colour Test provided results significantly ($p < 0.001$) more rapidly than the IPM or MGIT assays. Colour Test accuracy compared to MGIT DST for detecting isoniazid and rifampicin resistance and MDR-TB was 88% (95%CI = 81-96), 92% (95%CI = 86-98), and 94% (95%CI = 88-99), respectively. Colour Test accuracy compared to IPM to detect isoniazid, rifampicin resistance and MDR-TB was 92% (95%CI = 86-98), 81% (95%CI = 72-90), and 90% (95%CI = 83-96). IPM test accuracy compared to MGIT DST for detecting isoniazid and rifampicin resistance and MDR-TB was 91% (95%CI = 85-97), 83% (95%CI = 75-92), and 85% (95%CI = 77-93), respectively. Moxifloxacin drug-susceptibility testing could not be assessed because only two isolates showed evidence of resistance. Conclusion: The accuracy of Mtb drug-susceptibility testing was similar comparing: Colour Test versus IPM, Colour Test versus MGIT; and comparing IPM versus MGIT. The Colour Test was easy to use and determined drug-susceptibility significantly more rapidly than the IPM and MGIT assays. Thus, implementing the Colour Test in clinical settings could make drug-susceptibility testing more accessible and rapid in high TB burden, and resource-constrained settings, including in Ethiopia.

DOI: 10.21203/rs.3.rs-6697928/v1
PMCID: PMC12270243
PMID: 40678234

4. Long term outcomes in drug resistant tuberculosis with Bedaquiline, Pretomanid and varying doses of Linezolid.

J Infect. 2025 Jul;91(1):106509. doi: 10.1016/j.jinf.2025.106509. Epub 2025 May 15.

Daniel BD(1), Shanmugam S(2), Mehta R(3), Bhalla M(4), Mariappan M(2), Ramraj B(5), Awasthi AK(6), Patel P(7), Jain A(8), Jain P(8), Kumar C(9), Oswal V(10), Singla N(4), Kumar S(11), Dave J(12), Vadgama P(13), Bhatnagar AK(14), Kant S(8), Prabhakaran R(15), Tamakuwala G(13), Mukherjee RN(14), Santhanakrishnan RK(2), Ravikumar D(2), Nagarajan NK(2), Kumaravadivelu S(2), Bharathi J(2), Sridhar A(16), Ramachandran R(16), Matoo SK(17), Ponnuraja C(2), Jaju J(18), Padmapriyadarsini C(2).

Author information:
(1)ICMR - National Institute for Research in Tuberculosis, Chennai, Tamil Nadu, India. Electronic address: belladevalleenal.d@icmr.gov.in.
(2)ICMR - National Institute for Research in Tuberculosis, Chennai, Tamil Nadu, India.
(3)Infexn laboratories Private Ltd, Mumbai, Maharashtra, India.
(4)National Institute of Tuberculosis and Respiratory Diseases, New Delhi, India.
(5)ICMR - National Institute for Research in Tuberculosis, Chennai, Tamil Nadu, India. Electronic address: balaji.ramraj@icmr.gov.in.
(6)Intermediate Reference Laboratory, NTEP, State TB Training & Demonstration Centre, Agra, Uttar Pradesh, India.
(7)Intermediate Reference Laboratory, NTEP, Ahmedabad, Gujarat, India.
(8)King George's Medical University, Lucknow, Uttar Pradesh, India.
(9)Sarvodaya Charitable Trust Hospital, Mumbai, Maharashtra, India.
(10)Shatabdi Centenary Hospital, Mumbai, Maharashtra, India.
(11)SN Medical College, Agra, Uttar Pradesh, India.
(12)Government Medical College, Bhavnagar, Gujarat, India.
(13)Government Medical College, Surat, Gujarat, India.
(14)Rajan Babu Institute of Pulmonary Medicine and Tuberculosis, New Delhi, India.
(15)Government Rajaji Hospital, Madurai Medical College, Madurai, Tamil Nadu, India.

(16)World Health Organization, India Office, New Delhi, India.
(17)National Tuberculosis Elimination Programme, Central TB Division, New Delhi, India.
(18)iDEFEAT TB project, International Union Against Tuberculosis and Lung Disease, New Delhi, India.

OBJECTIVES: Assess the effectiveness of bedaquiline, pretomanid and linezolid (BPaL) regimens with varying doses and duration of linezolid at the end of 48 weeks post treatment among drug resistant tuberculosis (DR TB) patients.
METHODS: Multicentric pragmatic randomized clinical trial in which BPaL regimens were given for 26 weeks for pulmonary pre extensively drug resistant tuberculosis (PreXDR TB); bedaquiline, pretomanid and linezolid 600 mg for 26 weeks (arm1), structured dose reduction arms with linezolid dose reduction from 600 to 300 mg after nine weeks (arm2) and 13 weeks (arm3). Participants were followed up for recurrence-free cure up to 48 weeks post-treatment. Whole genome sequencing in sputum samples at baseline and recurrence differentiated relapse and reinfection.
RESULTS: Of 403 enrolled, 378 were included for the modified intent-to-treat analysis based on baseline sputum culture positivity and sensitivity to medications in the study regimen. Among them, 331(88%) had recurrence-free cure at the end of 48 weeks of post-treatment follow-up; arm1:112(87%), arm2:110(88%), arm3:109(88%). Overall, 14 (12 bacteriological and 2 clinical) recurrences (arm1-four, 2-six and 3-four) occurred; 11 recurrences occurred within 24 weeks after treatment completion; four out of 11 within the first 12 weeks. Of the 10 paired sputum samples available at baseline and recurrence for comparison of lineages, there were two reinfections and eight relapses.
CONCLUSION: Structured dose reduction arms had comparable recurrence free cure rates as linezolid 600 mg arm when given along with bedaquiline and pretomanid for 26 weeks in PreXDR TB. Most of the recurrences occurred within the first six months.

DOI: 10.1016/j.jinf.2025.106509
PMCID: PMC12170348
PMID: 40381662 [Indexed for MEDLINE]

5.Epidemiology of drug-resistant tuberculosis among hospitalized children with tuberculosis in southwest China, 2017-2024.

Front Microbiol. 2025 Jul 2;16:1609146. doi: 10.3389/fmicb.2025.1609146. eCollection 2025.

Wang DM(1), An Q(1), Yang Q(1), Liao Y(2).

Author information:
(1)Department of Science and Education Division, Public Health Clinical Center of Chengdu, Chengdu, China.
(2)Department of Clinical Laboratory Medicine, Chengdu Women's and Children's Central Hospital, School of Medicine, University of Electronic Science and Technology of China, Chengdu, China.

BACKGROUND: To describe the demographic and clinical characteristics of pediatric tuberculosis (TB) inpatients diagnosed with resistance to any anti-tuberculosis drug [drug-resistant tuberculosis (DR-TB)] in southwest China.
METHODS: Patients aged ≤14 years with clinically diagnosed pediatric TB were recruited from January 2017 to December 2024 at specialty hospitals in southwest China based on either etiology or clinical confirmation. Hospitalization records were extracted for each patient.
RESULTS: Among 2,208 pediatric TB patients, 90 (4.08%) had DR-TB. DR-TB cases had an average age of 10.94 ± 3.52 years, with a male-to-female ratio of 0.76:1. The highest proportion was in the 10-14-year age group (72.2%), and prevalence was significantly higher in girls than boys. By disease type, 13.33% had pulmonary tuberculosis, 5.56% had extrapulmonary tuberculosis (EPTB), and 81.11% had combined TB. The most common form of EPTB was lymph node TB (30.00%), followed by pleural TB (20.71%), abdominal TB (19.29%), and TB meningitis (14.29%). Among the 90 pediatric DR-TB cases, 74.4% were primary patients (with rifampicin-resistant TB and multidrug-resistant TB accounting for 36.7 and 30.0%, respectively). The Tibetan ethnic group had the highest proportion of DR-TB cases (63.3%). Over the 8-year period, most pediatric DR-TB cases were from western Sichuan (including Ganzi, Aba, and Liangshan minority areas), with the highest number in the Ganzi Tibetan Autonomous Prefecture.
CONCLUSION: Pediatric DR-TB in southwest China predominantly affects older girls, with primary cases representing a high proportion. The western regions of Sichuan bear a relatively high burden. Public health efforts should prioritize awareness, screening, and early diagnosis of pediatric DR-TB in high-risk areas to prevent transmission.

DOI: 10.3389/fmicb.2025.1609146
PMCID: PMC12263897
PMID: 40673150

Conflict of interest statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could

be construed as a potential conflict of interest.

6. Cycloserine resistance among drug-resistant tuberculosis cases in Taiwan.

Microbiol Spectr. 2025 Jul;13(7):e0342224. doi: 10.1128/spectrum.03422-24. Epub 2025 Jun 9.

Wu S-H(#)(1)(2), Liu H-Y(#)(1)(2), Liu K-H(1)(2), Hsiao H-C(1)(2), Jou R(1)(2).

Author information:
(1)Tuberculosis Research Center, Centers for Disease Control, Ministry of Health and Welfare, Taipei, Taiwan.
(2)Reference Laboratory of Mycobacteriology, Centers for Disease Control, Ministry of Health and Welfare, Taipei, Taiwan.
(#)Contributed equally

Cycloserine (CS) is a widely used drug for drug-resistant tuberculosis (DR-TB) treatment. The World Health Organization (WHO) recently suggested a critical concentration (CC) for CS using the MGIT 960 system (MGIT). To strengthen our DR-TB management program, we performed CS resistance analyses to provide comprehensive drug susceptibility testing (DST). This retrospective study included Mycobacterium tuberculosis complex (MTBC) isolates obtained from 114 rifampin-resistant (RR) and multidrug-resistant (MDR) TB cases. We compared the results of phenotypic DST (pDST) and genotypic DST (gDST) and evaluated the minimum inhibitory concentration (MIC) using both MGIT and the Sensititre MYCOTB MIC Plate (Sensititre). Sanger sequencing and whole-genome sequencing were conducted to analyze the mutations of CS-resistant-associated ald and alr genes. Our results indicated that the optimal consistency with gDST was achieved with the CC of 16 µg/mL for MGIT, which aligns with the WHO recommendations, and the CC of 8 µg/mL for Sensititre. Of the 114 MTBC isolates, we found 5 (4.4%) CS-MGIT-resistant isolates, which all harbored mutations in the alr gene, including three previously known mutations M343T, T20M, L113R, and a novel mutation R243S, whereas seven low-MIC isolates harboring alr Q30R mutations might not be associated with CS resistance. Notably, M1I, E118K, and A184T in the ald gene and L113R, R243S, S261N, and M343T in the alr gene were predicted to have a destabilizing effect, which could interfere with protein functions and induce drug resistance. For accurate routine diagnosis of CS susceptibility, we adopted the CC of 16 µg/mL and suggested an interim 8 µg/mL using MGIT and Sensititre, respectively.IMPORTANCETo strengthen the DR-TB management program in Taiwan, we performed cycloserine (CS) resistance analyses to enhance treatment outcomes. Of the 114 drug-resistant tuberculosis (DR-TB) isolates, we found 5

(4.4%) CS-MGIT-resistant isolates, with four isolates classified as multidrug-resistant (MDR)-TB and one isolate as Pre-XDR-TB. In addition, we observed all CS-MGIT-resistant isolates harbored mutations in the alr gene, including three previously known high-confidence mutations M343T, T20M, and L113R, as well as the novel R243S mutation. We also found that mutations could lead to CS resistance by disrupting protein stability.

DOI: 10.1128/spectrum.03422-24
PMCID: PMC12211041
PMID: 40488463 [Indexed for MEDLINE]

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

7. Advances and prospects for treatment strategies of drug-resistant tuberculosis: a review.

GMS Hyg Infect Control. 2025 Jun 26;20:Doc33. doi: 10.3205/dgkh000562. eCollection 2025.

Michalik M(1), Lorenc T(1), Marcinkowski K(2), Muras M(3), Mikszta N(4), Mikszta J(4), Kantor K(5), Marcinkowska J(5).

Author information:
(1)Warsaw Southern Hospital, Warsaw, Poland.
(2)Ludwik Rydygier Specialist Hospital, Cracow, Poland.
(3)Provincial Specialist Hospital Nr 2, Jastrzebie-Zdroj, Poland.
(4)Provincial Specialist Hospital Nr 3, Rybnik, Poland.
(5)Faculty of Medical Sciences in Katowice, Medical University of Silesia, Katowice, Poland.

Drug-resistant tuberculosis (DR-TB) poses a significant global health threat, particularly in low- and middle-income countries with limited access to quality healthcare. By 2023, 10% of global tuberculosis cases were classified as drug-resistant, with multidrug-resistant (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) showing increasing prevalence. The treatment of DR-TB has been complicated by long regimens, severe side effects and high overall costs, which contribute to non-adherence and treatment failures. Novel pharmacological agents including bedaquiline, linezolid, meropenem and more, have shown promise in improving treatment outcomes, shortening therapy duration, and enhancing patient compliance. These drugs have demonstrated effectiveness in both MDR-TB and XDR-TB cases, particularly when used in combination therapies as BPaLM (the combination of bedaquiline, pretomanid, linezolid and moxifloxacin). However,

challenges remain, including limited access to drugs, diagnostic tools, and healthcare infrastructure, particularly in high-burden regions. Although regimens incorporating these agents offer improved treatment success rates, they require careful monitoring due to potential side effects and the risk of resistance. Future research should focus on refining these regimens, optimizing drug use for resource-limited settings, and addressing logistical and economic barriers to ensure more effective and accessible treatment. The ultimate goal is to reduce the global burden of DR-TB and improve outcomes for affected populations.

Publisher: Die arzneimittelresistente Tuberkulose (DR-TB) stellt eine erhebliche globale Gesundheitsbedrohung dar, insbesondere in Ländern mit niedrigem und mittlerem Einkommen, die begrenzten Zugang zu hochwertiger Gesundheitsversorgung haben. Bis 2023 wurden 10% der weltweiten Tuberkulosefälle als arzneimittelresistent eingestuft, wobei die Prävalenz von multiresistenter (MDR-TB) und extensiv arzneimittelresistenter Tuberkulose (XDR-TB) zunimmt. Die Behandlung der DR-TB wird durch langwierige Therapieschemata, schwere Nebenwirkungen und hohe Gesamtkosten erschwert, was zu mangelnder Therapieadhärenz und Behandlungsversagen führt. Neuartige pharmakologische Wirkstoffe wie Bedaquilin, Linezolid, Meropenem und andere haben vielversprechende Ergebnisse hinsichtlich der Verbesserung der Therapieergebnisse, der Verkürzung der Therapiedauer und der Erhöhung der Patientenzufriedenheit gezeigt. Insbesondere in Form von Kombinationstherapien wie BPaLM (die Kombination von Bedaquilin, Pretomanid, Linezolid und moxifloxacin) haben sich diese Medikamente bei MDR-TB- und XDR-TB-Fällen als wirksam erwiesen. Dennoch bestehen weiterhin Herausforderungen durch eingeschränkten Zugang zu Medikamenten, Diagnosetools und medizinischer Infrastruktur, insbesondere in Regionen mit hoher Krankheitslast. Obwohl Therapieschemata, die diese Wirkstoffe integrieren, höhere Erfolgsraten bieten, erfordern sie eine sorgfältige Überwachung aufgrund potenzieller Nebenwirkungen und des Risikos der Resistenzentwicklung. Zukünftige Forschung sollte darauf abzielen, die Situation zu optimieren, den Einsatz von Medikamenten in ressourcenarmen Umgebungen zu verbessern und logistische sowie wirtschaftliche Barrieren anzugehen, um effektivere und zugänglichere Behandlungen sicherzustellen. Das übergeordnete Ziel bleibt die Reduktion der globalen DR-TB-Belastung und die Verbesserung der Behandlungsergebnisse für die betroffenen Bevölkerungsgruppen.

DOI: 10.3205/dgkh000562
PMCID: PMC12248249
PMID: 40657634

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

8.From Repurposing to Refinement: Optimizing Levofloxacin for Treatment of Multidrug-Resistant Tuberculosis.

Am J Respir Crit Care Med. 2025 Jul;211(7):1126-1127. doi: 10.1164/rccm.202503-0550ED.

Yim JJ(1).

Author information:
(1)Department of Internal Medicine Seoul National University College of Medicine Seoul, Republic of Korea.

Comment on
Am J Respir Crit Care Med. 2025 Jul;211(7):1277-1287. doi: 10.1164/rccm.202407-1354OC.

DOI: 10.1164/rccm.202503-0550ED
PMCID: PMC12264645
PMID: 40315145

9.Sociodemographic determinants of multidrug-resistant tuberculosis in Lesotho: A case-control study.

PLOS Glob Public Health. 2025 Jul 10;5(7):e0004075. doi: 10.1371/journal.pgph.0004075. eCollection 2025.

Yahaya JY(1).

Author information:
(1)Technical Services Division, Ghana AIDS Commission, Accra, Ghana.

The emergence of multidrug-resistant tuberculosis (MDR-TB) significantly undermines global efforts toward tuberculosis (TB) control, particularly in high-burden settings like Lesotho. Understanding the sociodemographic factors contributing to MDR-TB is crucial yet remains under-explored in this context. This study aimed to identify key sociodemographic determinants associated with MDR-TB among adult TB patients in Lesotho. Using a retrospective case-control

design, I analyzed data from 306 participants, including confirmed MDR-TB cases and drug-susceptible TB controls, recruited from 12 TB clinics between March 2021 and February 2022. Sociodemographic characteristics (age, sex, education, employment, income, place of residence), HIV status, and caregiver presence were examined using chi-square tests and multivariable logistic regression analyses. The findings indicated that individuals older than 26 years had lower odds of MDR-TB compared to those aged 18-26 years (OR = 0.8, 95% CI 0.67-0.99, p = 0.040). Similarly, higher income levels (earning more than $1,026 annually) were associated with reduced odds of MDR-TB (OR = 0.5, 95% CI 0.22-0.94, p = 0.034). Conversely, the absence of caregiver support significantly increased the likelihood of MDR-TB by 80% (OR = 1.8, 95% CI 1.04-3.11, p = 0.036). These findings highlight the critical need for targeted interventions focusing on socioeconomic empowerment, caregiver support, and tailored public health education to effectively mitigate the MDR-TB burden in Lesotho.

DOI: 10.1371/journal.pgph.0004075
PMCID: PMC12244824
PMID: 40638609

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

10.The Ethiopian Third National Tuberculosis Drug Resistance Survey Incorporating Whole Genome Sequencing.

Open Forum Infect Dis. 2025 Jul 21;12(7):ofaf367. doi: 10.1093/ofid/ofaf367. eCollection 2025 Jul.

Moga S(1), Getahun M(1), Mohammed Z(1), Alemu A(1), Diriba G(1), Yenew B(1), Fikadu D(1), Abebaw Y(1), Amare M(1), Tesfaye E(1), Kebede A(1), Yaregal Z(1), Meaza A(1), Mollalign H(1), Dagne B(1), Tadesse M(1), Sinshaw W(1), Seid G(1), Zerihun B(1), Getu M(1), Tadesse G(1), Abdella S(2), Tollera G(3), Admas A(4), Yilma A(5), Molla Y(6), Mikru F(5), Assefa D(6), Girma T(7), Feleke B(7), Di Marco F(8), Cirillo DM(8), Dean A(9), Maurizio Cabibbe A(8), Klinkenberg E(6)(9)(10).

Author information:

(1)Infectious Diseases Research Directorate, Ethiopian Public Health Institute, Addis Ababa, Ethiopia.
(2)Health Laboratory Services, Ethiopian Public Health Institute, Addis Ababa, Ethiopia.
(3)Public Health Research, Ethiopian Public Health Institute, Addis Ababa, Ethiopia.
(4)National TB and Leprosy Control Program, Ministry of Health, Addis Ababa, Ethiopia.
(5)Country Office for Ethiopia, World Health Organization, Addis Ababa, Ethiopia.
(6)Challenge TB Project, United States Agency for International Development, Addis Ababa, Ethiopia.
(7)Division of Global HIV and Tuberculosis, US Centers for Disease Control and Prevention, Addis Ababa, Ethiopia.
(8)Division of Immunology, Transplantation, and Infectious Diseases, IRCCS San Raffaele Scientific Institute, Milan, Italy.
(9)Global TB Program, World Health Organization, Geneva, Switzerland.
(10)Department of Global Health, Amsterdam University Medical Centers, Amsterdam, The Netherlands.

BACKGROUND: Drug-resistant tuberculosis (DR-TB) is a major challenge hindering global tuberculosis control. Ethiopia conducted a third national antituberculosis (TB) drug resistance survey, and this is the first survey to report on drug resistance using whole genome sequencing (WGS) in addition to genotypic and phenotypic test results. The aim of this study was to obtain up-to-date information regarding the magnitude and pattern of drug resistance in Ethiopia.
METHODS: A nationwide cross-sectional study was conducted in 217 health facilities across all Ethiopian regional states from August 2017 to January 2019. Sputum specimens were collected from patients with bacteriologically confirmed pulmonary TB to detect resistance to anti-TB drugs with Xpert MTB/RIF assay, culture-based phenotypic drug susceptibility testing (DST), and WGS with phylogenetic analysis.
RESULTS: The prevalence of rifampicin-resistant TB (RR-TB) was 1.07% (95% confidence interval [CI], .65%-1.74%) among new cases and 6.89% (95% CI, 4.02%-11.57%) among previously treated cases. The prevalence of isoniazid-resistant, rifampicin-susceptible TB was 4.15% (95% CI, 3.11%-5.53%) among new cases and 4.41% (95% CI, 1.97%-9.57%) among previously treated cases. While resistance to fluoroquinolones was detected in 1 RR-TB case, resistance to bedaquiline and linezolid was not detected in RR-TB cases. Mycobacterium tuberculosis lineage 4 was the most common, followed by lineage 3 and lineage 1, with sublineage 4.2.2 being the most frequent.
CONCLUSIONS: The level of RR-TB remained low. Expanding baseline DST for isoniazid may help further lower the burden of DR-TB in Ethiopia.

DOI: 10.1093/ofid/ofaf367
PMCID: PMC12278268
PMID: 40693102

Conflict of interest statement: Potential conflicts of interest. All authors report no potential conflicts.

11. Ration or compassion? Stakeholder perspectives on the introduction of bedaquiline in South Africa.

PLOS Glob Public Health. 2025 Jul 18;5(7):e0004821. doi: 10.1371/journal.pgph.0004821. eCollection 2025.

Raad R(1), Hoddinott G(2)(3), Gorsky M(4), Dixon J(1)(5).

Author information:
(1)Department of Global Health and Development, Faculty of Public Health and Policy, London School of Hygiene and Tropical Medicine, London, United Kingdom.
(2)Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa.
(3)School of Public Health, Faculty of Medicine and Health, University of Sydney, Camperdown, New South Wales, Australia.
(4)Centre for History in Public Health, Faculty of Public Health and Policy, London School of Hygiene and Tropical Medicine, London, United Kingdom.
(5)The Health Research Institute Zimbabwe, Biomedical Research and Training Institute, Harare, Zimbabwe.

Antimicrobial resistance (AMR) is a global health emergency that poses a significant challenge to disease control efforts that rely on antibiotics. Drug-resistant tuberculosis (DR-TB) is a major contributor to global AMR, but its management has historically often remained confined to TB-specific discussions. The emergence of bedaquiline (BDQ), the first novel TB drug in decades, is a moment of potential confluence between AMR and DR-TB. By examining the period between 2012 and 2018, when BDQ was made available for DR-TB in South Africa, this study explores how the introduction of this novel drug foregrounded tensions between antimicrobial access and stewardship in resource-constrained settings. Through qualitative interviews with doctors, policymakers, patients, and activists in the context of DR-TB policy, programming, and care delivery, we

explore how these stakeholders balanced the imperative to expand access to this critical new antibiotic and the imperative to ensure its longevity. South Africa, we show, adopted a liberal approach to access to BDQ, grounded in a compassionate care approach that represented a significant shift from the country's traditional drug rationing aimed at mitigating the spread of DR-TB. We document the numerous obstacles that were faced in enabling compassionate use, as well as the broader implications of South Africa's liberal BDQ policy both for TB management in South Africa and for global AMR strategies. The BDQ experience suggests that integrating compassionate care into stewardship models can yield positive public health outcomes, challenging some of the foundational assumptions underlying stewardship. In the process, it suggests that a third, balanced strategy is available that explicitly integrates equitable access with robust stewardship to fulfil both immediate and long-term public health goals.

DOI: 10.1371/journal.pgph.0004821
PMCID: PMC12273958
PMID: 40680035

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

12. Prevalence and Determinants of Drug-Resistant Tuberculosis (DR-TB) Among Tuberculosis Patients in Pokhara Metropolitan City, Gandaki Province, Nepal.

Interdiscip Perspect Infect Dis. 2025 Jul 7;2025:3730719. doi: 10.1155/ipid/3730719. eCollection 2025.

Sah SK(1), Pyakurel CK(2), Kathariya A(2), Shrestha A(2), Subedi NK(2), Byanjankar N(2), Basnet R(3).

Author information:
(1)Department of Pharmacy, Institute of Medicine (IOM), Maharajgunj Medical Campus (MMC), Tribhuvan University, Kathmandu, Nepal.
(2)Department of Pharmacy, Little Buddha College of Health Science, Purbanchal University, Kathmandu, Nepal.
(3)Central Department of Public Health (CDPH), Institute of Medicine (IOM),

Tribhuvan University, Kathmandu, Nepal.

Background: Drug-resistant tuberculosis (DR-TB) remains a significant global public health challenge, particularly in regions with a high burden of TB. Nepal, one such country, has been witnessing a rise in DR-TB cases, posing serious challenges to TB control efforts. Despite this growing concern, there is a lack of localized data on the risk factors contributing to DR-TB, especially in urban areas like Pokhara. This study aims to fill that gap by assessing the prevalence of DR-TB and identifying associated demographic, behavioral, and clinical factors among TB patients in Pokhara Metropolitan City, Gandaki Province, Nepal. Methods: A retrospective cross-sectional analysis was conducted using 617 TB patient records from the Pokhara Metropolitan Health Office for the fiscal year 2078/79 (July 2021 to July 2022). Data on demographic characteristics, clinical history, treatment regimens, and behavioral factors such as smoking and alcohol consumption were extracted. Descriptive statistics were used to determine the prevalence of DR-TB, and bivariate logistic regression was applied to identify statistically significant risk factors associated with DR-TB. Results: Among the 617 TB patients, the prevalence of DR-TB was 2.6%. Most patients were male (57.4%) and within the 21-30 age group (26.9%). Pulmonary bacteriologically confirmed TB was the most common type (53.6%), predominantly affecting adults (98.1%). The primary treatment regimen administered was 2HRZE + 4HR (78.8%). TB-HIV co-infection was found in 1.9% of cases, with all co-infected patients receiving antiretroviral therapy. In a bivariate analysis, individuals with current smoking status (UOR: 9.384; CI: 3.342-26.351), exposure to smoking (UOR: 8.550: CI: 2.916-25.064), and current alcohol consumption (UOR: 4.553, CI: 1.406-14.745) had a higher likelihood of DR-TB. In a multivariate analysis, exposure to smoking (AOR: 5.317; CI: 1.394-20.274) and current alcohol consumption (AOR: 6.84; CI: 2.071-22.58) emerged as independent predictors associated with an increased risk of DR-TB. Conclusion: The study revealed a relatively low prevalence of DR-TB among TB patients in Pokhara, with strong associations between DR-TB and lifestyle factors such as smoking and alcohol use. These findings underscore the need for targeted public health interventions addressing behavioral risk factors to reduce DR-TB incidence. Enhanced surveillance, public awareness, and preventive strategies should be integrated into TB control programs to mitigate the spread of DR-TB in this region. Moreover, targeted behavioral interventions may be crucial in curbing the emergence of DR-TB, particularly in high-burden urban centers.

DOI: 10.1155/ipid/3730719
PMCID: PMC12259324

PMID: 40661876

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

13. The mutant selection window of moxifloxacin and bedaquiline resistant Mycobacterium tuberculosis.

J Infect. 2025 Jul;91(1):106523. doi: 10.1016/j.jinf.2025.106523. Epub 2025 May 30.

Sonnenkalb L(1), Trubenová B(2), Regoes RR(3), Merker M(4), Niemann S(5).

Author information:
(1)Molecular and Experimental Mycobacteriology, Research Center Borstel, Leibniz Lung Center, Parkallee 1-40, 23845 Borstel, Germany; German Centre for Infection Research (DZIF), Partner Site Hamburg-Lübeck-Borstel-Riems, Borstel, Germany. Electronic address: lsonnenkalb@fz-borstel.de.
(2)Institute of Integrative Biology, ETH Zurich, Zurich, Switzerland; Department of Aquatic Ecology, Swiss Federal Institute of Aquatic Science and Technology (Eawag), Dübendorf, Switzerland.
(3)Institute of Integrative Biology, ETH Zurich, Zurich, Switzerland.
(4)Evolution of the Resistome, Research Center Borstel Leibniz Lung Center, Parkallee 1, 23845 Borstel, Germany.
(5)Molecular and Experimental Mycobacteriology, Research Center Borstel, Leibniz Lung Center, Parkallee 1-40, 23845 Borstel, Germany; German Centre for Infection Research (DZIF), Partner Site Hamburg-Lübeck-Borstel-Riems, Borstel, Germany; National Reference Center, Research Center Borstel Leibniz Lung Center, Parkallee 38, 23845 Borstel, Germany; EPHE, PSL University, 57 Rue Cuvier, 75005 Paris, France; Institutde Systématique, Evolution, Biodiversité, ISYEB, Muséum National d'Histoirenaturelle, CNRS, Sorbonne Université, EPHE, Université des Antilles, 57 Rue Cuvier, 75005 Paris, France. Electronic address: sniemann@fz-borstel.de.

Global health is threatened by the rise of antibiotic resistance. Bacteria of the Mycobacterium tuberculosis complex (Mtbc) are a major contributor to this antibiotic crisis, with about 450,000 new multidrug-resistant tuberculosis (MDR-TB) cases per year. This study investigates resistance evolution by defining the resistance mutant selection window (MSW) for the important MDR-TB treatment drugs moxifloxacin and bedaquiline. We employed a combination of long-term in vitro experiments supplemented with mathematical modeling that combined pharmacodynamics with population genetics. We assessed resistance selection at concentrations below the minimum inhibitory concentration (MIC),

the MSW and fitness cost of eight mutant clones with different resistance-associated variants. Both computational and experimental results show that mutant clone populations are selected far below the MIC, leading to a major growth advantage of resistant populations under weak selection pressure. An eighth of the MIC was enough to enrich mutant clone populations in the short term (five bacterial passages or 20 generations), even in mutant clones with a major competitive fitness loss. In fact, gyrA, gyrB and most Rv0678 mutations have virtually no effect on the bacteria's competitive fitness in vitro. This work highlights the risk that ineffective drug delivery and dosing can lead to the emergence of resistance.

DOI: 10.1016/j.jinf.2025.106523
PMID: 40451520 [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.

14.Trehalose catalytic shift inherently enhances phenotypic heterogeneity and multidrug resistance in Mycobacterium tuberculosis.

Nat Commun. 2025 Jul 11;16(1):6442. doi: 10.1038/s41467-025-61703-3.

Lee JJ(1), Swanson DH(2), Lee SK(3), Dihardjo S(1), Lee GY(1), Gelle S(1), Seong HJ(4), Bravo ERM(2), Taylor ZE(5), Van Nieuwenhze MS(5), Singh A(6), Lee JS(4), Eum S(4), Cho S(4), Swarts BM(2), Eoh H(7)(8).

Author information:
(1)Department of Molecular Microbiology and Immunology, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA.
(2)Department of Chemistry and Biochemistry, Central Michigan University, Mount Pleasant, MI, USA.
(3)Division of Immunology and Cellular Immunology, International Tuberculosis Research Center, Changwon, Republic of Korea.
(4)Department of Biological Science, Kunsan National University, Gunsan, Republic of Korea.
(5)Department of Chemistry and Biochemistry, Baylor University, Waco, TX, USA.
(6)Department of Electrical and Computer Engineering, Biomedical Engineering, Mathematical Sciences, University of Delaware, Newark, DE, USA.

(7)Department of Molecular Microbiology and Immunology, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA. heoh@usc.edu.
(8)Department of Ophthalmology, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA. heoh@usc.edu.

Update of
Res Sq. 2024 Sep 13:rs.3.rs-4999164. doi: 10.21203/rs.3.rs-4999164/v1.

Drug-resistance (DR) in bacteria often develops through the repetitive formation of drug-tolerant persisters, which survive antibiotics without genetic changes. It is unclear whether Mycobacterium tuberculosis (Mtb), the bacterium that causes tuberculosis (TB), undergoes a similar transitioning process. Recent studies highlight changes in trehalose metabolism as crucial for persister formation and drug resistance. Here, we observe that mutants lacking trehalose catalytic shift activity exhibited fewer DR mutants due to decreased persisters. This shift enhances Mtb survival during antibiotic treatment by increasing metabolic heterogeneity and drug tolerance, facilitating drug resistance. Rifampicin (RIF)-resistant bacilli display cross-resistance to other antibiotics linked to higher trehalose catalytic shift, explaining how multidrug resistance (MDR) can follow RIF-resistance. In particular, the HN878 W-Beijing strain exhibits higher trehalose catalytic shift, increasing MDR risk. Both genetic and pharmacological inactivation of this shift reduces persister formation and MDR development, suggesting trehalose catalytic shift as a potential therapeutic target to combat TB resistance.

DOI: 10.1038/s41467-025-61703-3
PMCID: PMC12254287
PMID: 40645928 [Indexed for MEDLINE]

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

15. Vitamin C potentiates the killing of Mycobacterium tuberculosis by bedaquiline through metabolic disruption.

mBio. 2025 Jun 25:e0148425. doi: 10.1128/mbio.01484-25. Online ahead of print.

Vilchèze C(1), Rajagopalan S(1), Kalluru RS(2), Banaei N(2), Jacobs WR Jr(1).

Author information:

(1)Department of Microbiology and Immunology, Albert Einstein College of Medicine, Bronx, New York, USA.
(2)Department of Pathology, Stanford University School of Medicine, Stanford, California, USA.

Tuberculosis (TB), a disease caused by the bacterium Mycobacterium tuberculosis (Mtb), continues to pose a major global health threat, exacerbated by the emergence of drug-resistant strains and the lengthy treatment regimens required for effective management. Bedaquiline (BDQ), a key component in novel regimens for multidrug-resistant (MDR) TB, has demonstrated significant efficacy but is threatened by rising resistance. Our study investigates the potential of vitamin C to enhance BDQ's activity and prevent resistance. We found that combining BDQ with vitamin C sterilized drug-susceptible and MDR Mtb cultures in vitro within 21 days, achieving a 6-log reduction in colony-forming units. This combination also enhanced Mtb killing in infected human macrophages and peripheral blood mononuclear cells. Transcriptomic analysis revealed that the BDQ/vitamin C combination induces widespread metabolic disruption in Mtb, characterized by upregulation of stress response and metal ion homeostasis genes and downregulation of energy metabolism and cell wall biosynthesis genes. Mechanistic studies implicated reactive oxygen species and disrupted copper homeostasis as contributing factors to the sterilization effect. These findings highlight the potential of using vitamin C as an adjunct therapy with BDQ, offering a promising strategy to enhance drug efficacy and mitigate emerging drug resistance during MDR-TB treatment.
IMPORTANCE: Tuberculosis (TB) remains a major global health problem, especially as drug-resistant forms become more common and harder to treat. Bedaquiline is one of the most important new drugs for treating these resistant infections, but resistance to bedaquiline is also starting to appear. This study found that the combination of vitamin C and bedaquiline sterilizes Mycobacterium tuberculosis cultures in vitro while potentiating bedaquiline activity in infected human macrophage cells. The combination appears to overwhelm the bacteria by creating stress and disrupting essential functions, like energy production and metal balance. These results suggest that vitamin C, a safe and inexpensive supplement, could be used alongside existing drugs to make treatment faster and more effective while also helping to prevent resistance.

DOI: 10.1128/mbio.01484-25
PMID: 40558048

16. Factors influencing the risk of developing multidrug-resistant pulmonary tuberculosis in Northeast Thailand.

J Clin Tuberc Other Mycobact Dis. 2025 Jul 2;40:100549. doi: 10.1016/j.jctube.2025.100549. eCollection 2025 Aug.

Leeka N(1), Laohasiriwong W(1), Mahato RK(1), Amprarat K(2), Chaisuksant S(3).

Author information:
(1)Faculty of Public Health, Khon Kaen University, Khon Kaen 40002, Thailand.
(2)Chum-Phae hospital Khon Kaen 40130, Thailand.
(3)Khon Kaen hospital, Khon Kaen 40000, Thailand.

BACKGROUND: This study aimed to identify the factors influencing Multidrug-Resistant Pulmonary Tuberculosis (MDR-TB) in Northeast Thailand.
METHODS: A case-control study was conducted by reviewing medical record and collecting primary data using a structured questionnaire. The study population comprised the case group of patients with MDR-TB and the control group consisted of other pulmonary tuberculosis patients aged 18 years and over with ratio 1 case: 3 controls. The factors influencing MDR-TB in the Northeast of Thailand were identified by multivariable analysis.
RESULTS: The results revealed that the majority of the cases and controls were males (73.79 % and 59.87 %, respectively) with mean ages of 50.50 years and 56.30 years. Cases had more moderate self-care behaviors (40.78 %) compared with controls (17.15 %). Nearly half (48.54 %) of the cases had a limited level of health literacy. Multivariable analysis demonstrated that education level (Adjusted Odd Ratio (AOR) = 1.12; 95 % CI = 1.14-1.96, p = 0.04), average monthly family income (AOR = 1.78; 95 % CI = 1.19-2.97, p = 0.01), number of windows (AOR = 2.03; 95 % CI = 1.34-3.91, p = 0.001), being diagnosed with tuberculosis two or more times (AOR = 4.63; 95 % CI = 2.51-12.35, p < 0.001), poor attitude towards tuberculosis illness (AOR = 1.32; 95 % CI = 1.05-2.48, p = 0.03), mild to moderate self-care behavior levels (AOR = 1.47; 95 % CI = 1.14-3.05, p < 0.001), and inadequate to problematic levels of health literacy (AOR = 2.11; 95 % CI = 1.36-3.63, p < 0.001) were significant determinants of MDR-TB.
CONCLUSIONS: This study concluded that education level, monthly family income, number of windows, recurrence of TB diagnosis, attitude towards TB illness, self-care behavior level and limited health literacy level were risk factors of MDR-TB. Inadequate health literacy was particularly associated with a high risk of developing MDR-TB. In order to increase treatment success rates, the results from this study should be used to improve targeted interventions and health education strategies.

DOI: 10.1016/j.jctube.2025.100549
PMCID: PMC12272133

PMID: 40688755

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

17. Unlocking potent anti-tuberculosis natural products through structure-activity relationship analysis.

Nat Prod Bioprospect. 2025 Jul 7;15(1):44. doi: 10.1007/s13659-025-00529-4.

Abdjul DB(1)(2), Budiyanto F(3), Wibowo JT(3), Murniasih T(3), Rahmawati SI(3), Indriani DW(3), Putra MY(3), Bayu A(4).

Author information:
(1)Research Center for Vaccine and Drugs, Research Organization for Health, National Research and Innovation Agency (BRIN), Jalan Raya Jakarta Bogor KM.46, Cibinong, Bogor, West Java, 16911, Indonesia. booby_abdjul@yahoo.com.
(2)North Sulawesi Research and Development Agency, Jalan 17 Agustus, Manado, North Sulawesi, 95116, Indonesia. booby_abdjul@yahoo.com.
(3)Research Center for Vaccine and Drugs, Research Organization for Health, National Research and Innovation Agency (BRIN), Jalan Raya Jakarta Bogor KM.46, Cibinong, Bogor, West Java, 16911, Indonesia.
(4)Research Center for Vaccine and Drugs, Research Organization for Health, National Research and Innovation Agency (BRIN), Jalan Raya Jakarta Bogor KM.46, Cibinong, Bogor, West Java, 16911, Indonesia. asep044@brin.go.id.

Tuberculosis (TB) remains a world health problem due to the high number of affected individuals, high mortality rates, prolonged treatment durations, and the increasing prevalence of resistance to commercial TB drugs. The emergence of resistance to anti-TB drugs has necessitated urgent research into drug discovery and development, focusing on novel mechanisms of action against Mycobacterium tuberculosis resistant strains. Natural products, with their remarkable structural diversity and bioactivity, are promising sources for the development of new TB drugs or the identification of potential chemical scaffolds exhibiting potent and novel biological activity with minimal or no cytotoxicity to host cells. This review focuses on potent anti-TB natural products with minimum inhibitory concentration (MIC) values below 5 µg mL-1 and examines their structure-activity relationship (SAR). Significant characteristics and relevant biological properties of each compound were analysed using a Random Forest, machine learning algorithm, to explore SAR. Using molecular docking, AutoDock Vina was utilised to assess molecular interactions with protein targets, and predictive accuracy was enhanced using the XGBoost machine learning model. These

analyses provide insights into the mode of action of these compounds and help identify key structural features contributing to their anti-TB activity. In addition, this review examines the correlation between the potency of selected anti-TB compounds and their cytotoxicity, offering valuable insights for the identification of promising scaffolds in TB drug discovery.

DOI: 10.1007/s13659-025-00529-4
PMCID: PMC12234934
PMID: 40622557

Conflict of interest statement: Declarations. Ethics approval and consent to participate: None of the authors of this article has performed studies involving animals in this article. Therefore, ethical declaration is not applicable for this work. Competing interests: 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.

18. Treatment outcomes of multi-drug-resistant and rifampicin-resistant tuberculosis with and without isolation of nontuberculous mycobacteria between 2018-2021: A retrospective cohort study in Ghana.

PLoS Negl Trop Dis. 2025 Jul 2;19(7):e0013204. doi: 10.1371/journal.pntd.0013204. eCollection 2025 Jul.

Abbew ET(1)(2)(3), Laryea R(4), Kwakye AO(2), Poku YA(5), Obiri-Yeboah D(6), Lynen L(1), Decroo T(1), Rigouts L(1)(3)(7), Lorent N(8)(9).

Author information:
(1)Department of Clinical Sciences, Institute of Tropical Medicine, Antwerp, Belgium.
(2)Department of Internal Medicine, Cape Coast Teaching Hospital, Cape Coast, Ghana.
(3)Department of Biomedical Sciences, University of Antwerp, Belgium.
(4)Eastern Regional Hospital, Koforidua, Ghana.
(5)National Tuberculosis Control Programme, Accra, Ghana.
(6)Department of Microbiology and Immunology, School of Medical Sciences, University of Cape Coast, Cape Coast, Ghana.
(7)Department of Biomedical Sciences, Institute of Tropical Medicine, Antwerp, Belgium.
(8)Department of Respiratory Diseases, University Hospital Leuven, Leuven, Belgium.

(9)Department of Chronic Diseases, Metabolism and Aging, BREATHE Laboratory, Katholieke Universiteit Leuven, Leuven, Belgium.

Multi-drug-resistant and rifampicin-resistant tuberculosis (MDR/RR-TB) pose an urgent health threat in Ghana. Despite ongoing interventions, the outcomes for MDR/RR-TB in Ghana have remained suboptimal over recent years. During this period, there has been an increasing detection of nontuberculous mycobacteria (NTM) in mycobacterial cultures. We sought to examine if the isolation of NTM could be a factor contributing to unfavourable MDR/RR-TB treatment outcomes. We also estimated predictors of NTM isolation, including using the short-course injectable-containing regimen (SCI) versus the all-oral bedaquiline (SCO) regimen and other covariates. This retrospective cohort study analysed MDR/RR-TB patients in Ghana from 2018 to 2021 across four regions. Demographic, clinical, and diagnostic data were collected under the National Tuberculosis Control Program framework. Mycobacterial smears and cultures were used to monitor treatment response, with further identification of NTM using line probe assays and Sanger sequencing. Multivariable logistic regression models evaluated predictors of NTM isolation and having an unfavourable outcome. Of 427 identified MDR/RR-TB patients, 380 were included for analysis: 76.3% were male, the mean age was 43.9 years, and 18.9% were people living with HIV. NTM were isolated in 7.1% of cases, primarily Mycobacterium intracellulare and M. fortuitum, with higher odds of isolation in individuals from the Eastern Region (aOR:14.18, 95% CI: 3.95-50.92). Overall, 67.9% achieved favourable outcomes: 71.4% (185/259) in those on the SCO versus 60.3% (73/121) on the SCI regimen. People living with HIV (aOR 14.18, 95% CI: 3.95-50.92) had an increased odds of having an unfavourable outcome. NTM isolation was not associated with unfavourable outcomes. Our study results suggest that although NTM isolation may occur during the course of MDR/RR-TB treatment, it does not affect MDR/RR-TB treatment outcome. Future research should further explore the implications of NTM co-infection on longer-term MDR/RR-TB outcomes, such as post-TB lung disease, to refine management strategies tailored to the reality of low-resource, high-burden settings.

DOI: 10.1371/journal.pntd.0013204
PMCID: PMC12221066
PMID: 40601698 [Indexed for MEDLINE]

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

19. Treatment outcomes in cavitary multidrug-resistant/rifampicin-resistant tuberculosis and risk factors for cavity closure: a retrospective cohort study in Southwest China.

Sci Rep. 2025 Jul 1;15(1):21302. doi: 10.1038/s41598-025-06080-z.

Chen Q(1), Zou L(2), Tang X(2), Huang T(2), Guo Z(2), Sun J(2), Lu X(2), Tang S(3), Wu G(4), He W(5).

Author information:
(1)Department of Tuberculosis, Public Health Clinical Center of Chengdu, Jingming 377 Street, Jingjiang District, Chengdu, 610061, Sichuan, China. doc_chen@sina.cn.
(2)Department of Tuberculosis, Public Health Clinical Center of Chengdu, Jingming 377 Street, Jingjiang District, Chengdu, 610061, Sichuan, China.
(3)Beijing Chest Hospital, Capital Medical University, Beijing Tuberculosis and Throcic Tumor Research Institute, Beijing, China.
(4)Department of Tuberculosis, Public Health Clinical Center of Chengdu, Jingming 377 Street, Jingjiang District, Chengdu, 610061, Sichuan, China. wghwgh2584@sina.com.
(5)Department of Tuberculosis, Public Health Clinical Center of Chengdu, Jingming 377 Street, Jingjiang District, Chengdu, 610061, Sichuan, China. gufuxiao_hw@163.com.

Pulmonary cavities in patients with tuberculosis contribute to antibiotic failure, transmission, morbidity, and mortality. We aimed to report the treatment outcomes and risk factors for cavity closure in cavitary multidrug-resistant/rifampicin-resistant tuberculosis in Southwest China. This study was a retrospective cohort study which included adult patients with multidrug-resistant /rifampicin-resistant tuberculosis in Southwest China from January 2018 to January 2023. The patients were categorized into cavity and non-cavity groups, and their clinical characteristics and treatment outcomes were retrospectively compared. A logistic regression model was used to identify potential risk factors associated with cavity closure. In this study, 305 patients were enrolled, with 223 cases in the cavity group and 82 cases in the non-cavity group. The median age of patients in the cavity group was 31 (24, 44) years, with a male to female sex ratio of 155/68. Within the cavity group, 8.1% of patients had rifampicin-resistant tuberculosis, 49.8% had multidrug-resistant tuberculosis, and 42.2% had pre-extensively-drug resistant tuberculosis. The treatment outcomes of the cavitary group showed that 48.9% of patients were cured, 28.3% completed treatment, 14.8% were lost to follow-up, and 6.7% could not be evaluated, with one failure and two deaths. Various factors such as male

gender, smoking, drinking, tuberculosis treatment history, baseline AFB smear, bilateral disease, and specific symptoms were more prevalent in the cavity group compared to the non-cavity group. Sputum culture conversion rates at 2 and 6 months were lower in the cavity group (25.6% vs 37.8%; 63.7% vs 79.3% ,all $P < 0.05$). Within patients with cavities, 40.6% experienced cavity closure after treatment, with a median closure time of 9.00 months. Baseline CD3+ T cell counts decreased was found to be an independent risk factor for cavity closure (aOR = 2.278, 95% CI 1.109-4.680, P = 0.025), while the use of a bedaquiline-containing regimen (aOR = 0.305, 95% CI 0.140-0.663, P = 0.003) and a delamanid-containing regimen (aOR = 0.260, 95% CI 0.086-0.785, P = 0.017) were protective factors. Cavities may influence the timing of culture conversion rather than influencing the treatment outcomes in patients with MDR/RR-TB. The use of bedaquiline and delamanid in treatment regimens for MDR/RR-TB patients could promote cavity closure and may enhance the management of cavitary MDR/RR-TB. Furthermore, the enhancement of immunotherapy could potentially contribute to reducing the burden of cavitary MDR/RR-TB.

DOI: 10.1038/s41598-025-06080-z
PMCID: PMC12214753
PMID: 40596245 [Indexed for MEDLINE]

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

20. Waste to worth: diagnostic accuracy of Xpert MTB/XDR on contaminated liquid cultures to salvage the detection of drug-resistant tuberculosis.

J Clin Microbiol. 2025 Jul 1:e0058025. doi: 10.1128/jcm.00580-25. Online ahead of print.

Ghebrekristos Y(#)(1)(2), Auma E(#)(1), Mahlobo Z(1), Venter R(1), Beylis N(3), Achar J(1)(4), Derendinger B(1), Singh S(1)(2), Burger M(2), Opperman C(1)(2)(3), Warren R(1), Theron G(1).

Author information:
(1)DSI-NRF Centre of Excellence for Biomedical Tuberculosis Research and SAMRC Centre for Tuberculosis Research, Division of Molecular Biology and Human Genetics, Faculty of Medicine and Health Sciences, Stellenbosch University, Tygerberg, Cape Town, South Africa.
(2)National Health Laboratory Service, Greenpoint Tuberculosis Laboratory, Cape

Town, South Africa.
(3)Division of Medical Microbiology, Department of Pathology, University of Cape Town, Cape Town, South Africa.
(4)Department of Global Public Health, Karolinska Institutet, Stockholm, Sweden.
(#)Contributed equally

Update of
Res Sq. 2025 Apr 12:rs.3.rs-6409041. doi: 10.21203/rs.3.rs-6409041/v1.

Mycobacterium Growth Indicator Tube (MGIT) 960 culture is critical for tuberculosis (TB) drug susceptibility testing (DST) but is vulnerable to contamination. We evaluated the accuracy of Xpert MTB/XDR, a molecular DST for isoniazid, fluoroquinolone, amikacin, and ethionamide, on to-be-discarded contaminated growth. Xpert MTB/XDR was applied to acid-fast-bacilli-negative, contaminated cultures from sputum from people with rifampicin-resistant TB when Xpert MTB/XDR on sputum was unsuccessful (not resistant or susceptible for all drugs), either at diagnosis (Cohort A) or during treatment monitoring (Cohort B). Future DSTs within 3 months served as a reference standard. We determined potential care cascade improvements. In Cohort A, 10% (66/650) of people had a contaminated culture; 89% (59/66) of contaminated growths were Xpert MTB/XDR TB-positive. Sensitivity and specificity for isoniazid, fluoroquinolone, amikacin, and ethionamide resistance were 100% (95% confidence interval [CI] 85, 100) and 100% (79, 100); 100% (59, 100) and 100% (89, 100); 100% (16, 100) and 100% (91, 100); and 100% (72, 100) and 96% (78, 100), respectively. In Cohort B, 22% (28/129) of people with a contaminated culture were Xpert MTB/XDR TB-positive. Of these, 57% (16/28), 7% (2/28), and 43% (12/28) were isoniazid-, fluoroquinolone-, and ethionamide-resistant (in two, one, and four people, respectively, this would be the first resistant result). In both cohorts, time-to-DST could improve by a median (IQR) of 22 (12-42) days. Xpert MTB/XDR on contaminated MGIT960 cultures had high sensitivity and specificity for DST. This approach could mitigate culture contamination's negative effects and improve gaps in the drug-resistant TB diagnostic cascade.
IMPORTANCE: Culture contamination is a common impediment to drug susceptibility testing for tuberculosis, the single biggest infectious cause of death globally. Xpert MTB/XDR is a World Health Organization-recommended rapid molecular test for second-line drug resistance. We evaluated Xpert MTB/XDR on contaminated liquid culture growth that would otherwise be discarded, with the people who provided these specimens potentially lost from care cascades. By applying Xpert MTB/XDR to contaminated growth in a high-volume programmatic laboratory, we found the number of people who had second-line DST improved, as did the number of resistant cases diagnosed and time to diagnosis. Furthermore, DST information was generated in people who otherwise would have had none. This approach can therefore reduce the effect of culture contamination on tuberculosis DST, permitting earlier diagnosis and effective treatment initiation and potentially

ultimately contributing to improving clinical outcomes and reducing transmission of drug-resistant TB.

DOI: 10.1128/jcm.00580-25
PMID: 40590556

21.An insight into the characterization of L2 Beijing multi-drug resistant tuberculosis: Description of resistance-associated-variants and discovery of Modern 7 L2 sublineage.

Infect Genet Evol. 2025 Jul 15:105797. doi: 10.1016/j.meegid.2025.105797. Online ahead of print.

Soutou MA(1), Allam C(2), Abifadel M(3), Najjar J(4), Guyeux C(5), Cambau E(6), Sola C(7).

Author information:
(1)INSERM, IAME, UMR1137, Université Paris Cité-Université Sorbonne-Paris Nord, 16, rue Henri-Huchard, cedex 18, BP 419, 75870 Paris, France; Service de mycobactériologie spécialisée et de référence, Laboratoire associé du Centre national de référence des mycobactéries et résistance des mycobactéries aux antituberculeux, APHP GHU Nord Université Paris Cité, Hôpital Bichat, 46, rue Henri Huchard, 75018 Paris, France; Laboratoire Rodolphe Mérieux Liban, Faculté de Pharmacie, Université Saint-Joseph de Beyrouth, Beyrouth, Lebanon. Electronic address: marianne.antar@usj.edu.lb.
(2)INSERM, IAME, UMR1137, Université Paris Cité-Université Sorbonne-Paris Nord, 16, rue Henri-Huchard, cedex 18, BP 419, 75870 Paris, France; Service de mycobactériologie spécialisée et de référence, Laboratoire associé du Centre national de référence des mycobactéries et résistance des mycobactéries aux antituberculeux, APHP GHU Nord Université Paris Cité, Hôpital Bichat, 46, rue Henri Huchard, 75018 Paris, France. Electronic address: camille.allam@aphp.fr.
(3)Laboratoire Rodolphe Mérieux Liban, Faculté de Pharmacie, Université Saint-Joseph de Beyrouth, Beyrouth, Lebanon. Electronic address: marianne.afibadel@usj.edu.lb.
(4)Fondation Mérieux, Beyrouth, Lebanon. Electronic address: josette.najjar@fondation-merieux.org.
(5)Université Marie et Louis Pasteur, Besançon, France. Electronic address: christophe.guyeux@univ-fcomte.fr.
(6)INSERM, IAME, UMR1137, Université Paris Cité-Université Sorbonne-Paris Nord, 16, rue Henri-Huchard, cedex 18, BP 419, 75870 Paris, France; Service de mycobactériologie spécialisée et de référence, Laboratoire associé du Centre national de référence des mycobactéries et résistance des mycobactéries aux

antituberculeux, APHP GHU Nord Université Paris Cité, Hôpital Bichat, 46, rue Henri Huchard, 75018 Paris, France. Electronic address: emmanuelle.cambau@aphp.fr.
(7)INSERM, IAME, UMR1137, Université Paris Cité-Université Sorbonne-Paris Nord, 16, rue Henri-Huchard, cedex 18, BP 419, 75870 Paris, France; Université Paris Saclay, Gif-sur-Yvette 91190, France. Electronic address: christophe.sola@universite-paris-saclay.fr.

Drug-resistant tuberculosis (TB) complicates global efforts toward TB elimination. However, the introduction of new and repurposed drugs- particularly the all-oral BPaL regimen (bedaquiline, pretomanid, and linezolid)-has raised hopes due to its favorable treatment outcomes for multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB. Susceptibility to these new drugs may vary depending on the lineage of the Mycobacterium tuberculosis (MTB) strain. Within the framework of a research project investigating the association between potential resistance-associated nucleotide variants and MTB lineages, we used the proprietary pipeline TB-Annotator to analyze 125,000 publicly available Short Read Archive datasets from NCBI. We identified 65 mutations across 65 clonal complexes of the lineage 2 (L2), that share at least one SNP within a list of 14 genes potentially involved in drug resistance to BPaL. During this large-scale genomic screening, we identified a previously uncharacterized clonal complex of 49 SRAs that did not belong to any previously described ancient or modern L2-sublineages (modern 1 to modern 6). We therefore performed a comparative genomic analysis on a representative set of L2 isolates to fully characterize this group. These 49 SRAs are found in an independent branch of the L2 phylogenetic tree. They share 4 SNPs, including an Ile-to-Leu substitution in the product of fbiD, and are organized into two subclusters, with an intra-sublineage SNP distance of around 150 ± 50 SNPs. We named this novel sublineage L2.2-M7. Further functional validation-through phenotypic drug susceptibility testing and gene replacement-is needed to determine whether this fbiD mutation confers resistance to pretomanid. Global genomic surveillance of this emerging sublineage is warranted to monitor its spread and clinical relevance in the era of new TB treatment regimens.

DOI: 10.1016/j.meegid.2025.105797
PMID: 40675313

Conflict of interest statement: Declaration of competing interest All authors declare that they have no conflict of interest. This study was partly supported by Fondation Mérieux, Lyon, France, through a grant support to Mrs. Marianne Antar Soutou. The authors declare that the founder did not have any influence in the investigation choices, nor on the management or on the decision to publish

or not the results of this research, that only reflects the opinion of the authors.

22. Global burden of tuberculosis among adults aged 60 years and older, 1990-2021: Findings from the global burden of disease study 2021.

Int J Infect Dis. 2025 Jun 26;158:107966. doi: 10.1016/j.ijid.2025.107966. Online ahead of print.

Liu J(1), Zhou Y(1), Guan J(1), Liu Y(1), Song W(1), Liu W(1), Yin X(1), Liu Y(2), Li T(2), Jin L(2), Zhang L(1), Li Y(1), Wu L(1), Wang N(1), Liu Z(1), Liu X(1), Wang Y(3), Wu Q(1), Liang L(4).

Author information:
(1)Department of Social Medicine, School of Health Management, Harbin Medical University, Harbin, 150081, China.
(2)Infectious Disease Hospital of Heilongjiang Province, Harbin, 150500, China.
(3)Heilongjiang Center for Disease Control and Prevention, Harbin, 150030, China.
(4)Department of Social Medicine, School of Health Management, Harbin Medical University, Harbin, 150081, China; Institute for Medical Demography, Harbin Medical University, Harbin, 150081, China. Electronic address: llbhit@163.com.

OBJECTIVES: Tuberculosis (TB) poses a significant threat to global public health, particularly, among elderly individuals. This study aimed to provide a comprehensive analysis of the patterns and temporal trends in the global disease burden of HIV-negative TB among adults aged ≥60 years from 1990 to 2021.
METHODS: Data on incidence, deaths, and disability-adjusted life-years of TB, drug-susceptible TB, multidrug-resistant TB (MDR-TB), and extensively drug-resistant TB (XDR-TB) were obtained from the Global Burden of Disease 2021. Frontier analysis was carried out to pinpoint areas for enhancement and disparities among nations stratified by development level. The Bayesian age-period-cohort model was used to forecast disease burden trends through 2035.
RESULTS: A decreasing trend in age-standardized incidence rate, age-standardized mortality rate, and disability-adjusted life-years rates for TB and drug-susceptible TB was observed among the elderly population worldwide, whereas an upward trend was noted for MDR-TB and XDR-TB. Frontier analyses revealed a potential for burden alleviation among diverse nations and regions, with high socio-demographic index nations, such as the Republic of Korea, showing higher disease burden than expected for their sociodemographic development. The Bayesian age-period-cohort model revealed that by 2035, the MDR-TB and XDR-TB burden will continue increasing in the elderly population.
CONCLUSIONS: The increasing MDR-TB and XDR-TB burden in older individuals

underscores the need for tailored interventions to combat TB burden, such as implementing active case finding among adults aged 60 years and older.

DOI: 10.1016/j.ijid.2025.107966
PMID: 40581250

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

23. Efficacy and Safety of Higher Doses of Levofloxacin for Multidrug-resistant Tuberculosis: A Randomized, Placebo-controlled Phase II Clinical Trial.

Am J Respir Crit Care Med. 2025 Jul;211(7):1277-1287. doi: 10.1164/rccm.202407-1354OC.

Phillips PPJ(1)(2), Peloquin CA(3), Sterling TR(4), Kaur P(5), Diacon AH(6), Gotuzzo E(7), Benator D(8), Warren RM(9), Sikes D(10), Lecca L(11), Gandhi NR(12), Streicher EM(9), Dianis N(13), Eisenach K(14), Mitnick CD(15), Horsburgh CR Jr(16).

Author information:
(1)UCSF Center for Tuberculosis and.
(2)Department of Medicine, University of California, San Francisco, San Francisco, California.
(3)College of Pharmacy and Emerging Pathogens Institute, University of Florida, Gainesville, Florida.
(4)Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee.
(5)Department of Global Health, Boston University School of Public Health, Boston, Massachusetts.
(6)TASK, Cape Town, South Africa.
(7)Instituto de Medicina Tropical Alexander von Humboldt, Universidad Peruana Cayetano Heredia, Lima, Peru.
(8)Infectious Diseases Section, Washington DC Veterans Affairs Medical Center, George Washington University, Washington, District of Columbia.
(9)Division of Molecular Biology and Human Genetics, Faculty of Medicine and Health Science, SAMRC Centre for Tuberculosis, Stellenbosch University, Cape Town, South Africa.
(10)Laboratory Branch, Division of Tuberculosis Elimination, Centers for Disease Control and Prevention, Atlanta, Georgia.
(11)Socios En Salud Sucursal Perú, Lima, Peru.

(12)Departments of Epidemiology, Global Health, and Medicine and Emory/Georgia Tuberculosis Research Advancement Center, Emory University, Atlanta, Georgia.
(13)Westat, Bethesda, Maryland.
(14)TB or NOT TB Consulting, LLC, Little Rock, Arkansas.
(15)Department of Global Health and Social Medicine, Harvard Medical School, Boston, Massachusetts; and.
(16)Departments of Epidemiology, Biostatistics, Global Health, and Medicine, Boston University Schools of Public Health and Medicine, Boston, Massachusetts.

Comment in
Am J Respir Crit Care Med. 2025 Jul;211(7):1126-1127. doi: 10.1164/rccm.202503-0550ED.

Rationale: Evaluation of optimal dosing has generally been inadequate during tuberculosis (TB) drug development. Fluoroquinolones are central to TB treatment. Objective: To determine the dose of levofloxacin needed to achieve maximal efficacy and acceptable safety and tolerability as part of a multidrug TB regimen. Methods: Opti-Q was an international, multicenter, randomized, placebo-controlled phase II trial. Eligible participants with TB resistant to isoniazid and rifampicin but susceptible to fluoroquinolones were randomized to receive one of four weight-adjusted once-daily doses of levofloxacin for 24 weeks (168 doses) alongside a multidrug regimen: 11 mg/kg (750 mg), 14 mg/kg (750 mg/1,000 mg), 17 mg/kg (1,000 mg/1,250 mg) or 20 mg/kg (1,250 mg/1,500 mg). The primary efficacy outcome was time to sputum culture conversion, and the primary safety outcome was grade ≥3 adverse events (AEs). Measurements and Main Results: A total of 111 participants were randomized from three sites in South Africa and Peru. Eighty-three (75%) had cavities on chest X-ray, 55 (50%) had a smear grading of 3+, and the median body mass index was 20.4 kg/m2. Median levofloxacin areas under the curve (AUCs)/minimum inhibitory concentrations were 573, 633, 918, and 1,343 across the four treatment arms. There was no difference in time to culture conversion on solid or liquid media by treatment arm (stratified log-rank P = 0.282), by tertile of AUC/minimum inhibitory concentration (P = 0.350), or by dose received (P = 0.723); 69.3%, 74.8%, 70.6%, and 78.3% exhibited culture conversion after 8 weeks on solid media, respectively, across the treatment arms; along with 64.6%, 69.5%, 52.6%, and 69.6% on liquid culture. More participants experienced a grade 3-5 AE at higher doses (37.0% and 16.0% in the highest and lowest dose groups, respectively; P = 0.042, Cochran-Armitage test for trend) and higher tertiles of AUC (P = 0.011). Conclusions: As part of a multidrug regimen, doses of levofloxacin >1,000 mg/d resulted in greater exposures and increased frequency of AEs but did not result in faster time to sputum culture conversion. A dose of 1,000 mg/d can achieve the target exposure in nearly all adults and was well tolerated. Clinical trial registered with www.clinicaltrials.gov (NCT01918397).

DOI: 10.1164/rccm.202407-1354OC
PMCID: PMC12213226
PMID: 40080768 [Indexed for MEDLINE]

24. Experimental dissection of tuberculosis protective immunity: a human perspective.

Front Cell Infect Microbiol. 2025 Jun 30;15:1595076. doi: 10.3389/fcimb.2025.1595076. eCollection 2025.

Schmidiger S(1)(2), Portevin D(1)(2).

Author information:
(1)Department of Medical Parasitology & Infection Biology, Swiss Tropical and Public Health Institute, Allschwil, Switzerland.
(2)Faculty of Science, University of Basel, Basel, Switzerland.

Mycobacterium tuberculosis (Mtb), the causative agent of tuberculosis (TB), has plagued humankind for millennia. Claiming 1.25 million lives in 2023, TB remains the worldwide leading cause of death from a single-infectious agent. Improved vaccines, diagnostics and treatment regimens for drug-susceptible and drug-resistant cases are paramount to attain the goals of the WHO's End TB Strategy. Our knowledge gap in protective immunity in TB impedes the development of such new vaccines and host-directed interventions. Mtb is a pathogen highly adapted to humans and primarily infects the lungs. Access to relevant specimens is invasive, preventing ample human TB studies, which therefore mostly rely on peripheral blood specimens and biopsies. Thus, there is a need for relevant surrogates. In recent years, in vivo, in vitro, and in silico systems have arisen to approach and model different aspects of TB pathogenesis. Moving away from cell-line infections and classical animal models, TB research has advanced to genetically diverse mice, 3D organoid cultures and computational modelling. We will review current TB models and discuss their applicability to decipher protective human immunity, understand disease progression, transmission, as well as evaluate vaccine candidates and unravel host-directed therapeutic approaches.

DOI: 10.3389/fcimb.2025.1595076
PMCID: PMC12256473
PMID: 40661970 [Indexed for MEDLINE]

Conflict of interest statement: The authors declare that the research was

conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

25. Real-world effectiveness and safety of prolonged bedaquiline course in the treatment of drug-resistant tuberculosis-a multi-center retrospective cohort study in a country with a high burden of drug-resistant tuberculosis.

Microbiol Spectr. 2025 Jul 7:e0009725. doi: 10.1128/spectrum.00097-25. Online ahead of print.

Yu Y(#)(1), Cao J(#)(1), Pan H(#)(2), Zhong H(3), Wu X(4), Yang J(4), Cheng L(1), Qu Q(1), Wang L(1), Lu F(2), Chen H(2), Wang J(3), Sha W(1), Sun Q(1).

Author information:
(1)Shanghai Clinical Research Center for Infectious Disease (Tuberculosis), Shanghai Key Laboratory of Tuberculosis, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai, China.
(2)Department of Tuberculosis, The Third People's Hospital of Zhenjiang affiliated to Jiangsu University, Zhenjiang, China.
(3)Department of Infectious Diseases, Shanghai Fengxian Guhua Hospital, Shanghai, China.
(4)Department of Clinical Laboratory, Shanghai Pulmonary Hospital affiliated to Tongji University, Shanghai, China.
(#)Contributed equally

Bedaquiline (BDQ) has gradually become a core drug in drug-resistant tuberculosis (DR-TB) treatment, and the additional benefits of prolonging BDQ use remain unclear. Patients with DR-TB who received a BDQ-containing regimen from three Chinese clinical centers between 1 March 2018 and 31 December 2021 were retrospectively analyzed. Treatment outcomes and adverse drug reactions were compared between 6-month and prolonged BDQ treatment group before and after adjustment by propensity score matching (PSM). A total of 160 patients were enrolled, 72 patients were treated with BDQ for 6 months, and 88 patients were over 6 months, of which the median duration was 9 months (IQR: 8-11 months). After PSM adjustment, there were no significant differences in treatment outcome between the prolonged groups (7-9, 10-12, >12 months) and the 6-month group (all $P > 0.05$). A total of 35 patients met the criteria for BDQ prolongation but did not receive it, resulting in a success rate of 60%, significantly lower than the prolonged group (78.4%, $P = 0.038$); however, after adjustment by PSM, there was no statistically significance ($P > 0.05$). The median treatment duration (23 months, IQR: 18.50-25.00 months) was significantly longer than the prolonged group (18 months, IQR: 15.00-20.25 months, $P < 0.001$). Additionally, two deaths

occurred in the prolonged group, and none in the 6-month group. The cause of death in one patient was adjudicated as anti-TB treatment-related, while the other one was considered not. There were no significant differences in the effectiveness and safety between 6-month and prolonged group, it's still recommended to prolong BDQ use under close monitoring when anti-TB drugs are insufficient to form an effective treatment regimen. Prolonged use of BDQ achieved similar treatment outcomes while potentially shortening the overall anti-TB duration.IMPORTANCEThis real-world retrospective cohort study provides critical evidence on the extended application of Bedaquiline (BDQ) in managing drug-resistant tuberculosis (DR-TB). To date, the effectiveness and safety data regarding prolonged BDQ treatment are still lacking, and the additional benefits of prolonged BDQ use remain unclear. Our findings notably demonstrate that prolonged use of BDQ can achieve similar treatment success rates while potentially shortening the overall anti-TB treatment duration. We conclude that when the anti-TB drugs are insufficient to form an effective treatment regimen, prolonged BDQ use with rigorous safety monitoring is recommended. Our study significantly advances the evidence base for prolonged use of BDQ in clinical practice.

DOI: 10.1128/spectrum.00097-25
PMID: 40621913

26. Prevalence and predictors of depression in tuberculosis patients in india: a systematic review and meta-analysis.

Discov Ment Health. 2025 Jul 12;5(1):104. doi: 10.1007/s44192-025-00248-9.

Samal J(1), Dehury RK(2), Thomas MB(3), Singh H(3).

Author information:
(1)School of Public Health, SRM Institute of Science and Technology, Kattankulathur, Tamil Nadu, India. janmejas@srmist.edu.in.
(2)School of Management Studies, University of Hyderabad, Hyderabad, Telangana, India.
(3)School of Public Health, SRM Institute of Science and Technology, Kattankulathur, Tamil Nadu, India.

INTRODUCTION: TB and common mental disorders pose significant global health challenges that considerably impact human health. The combination of depression with TB can lead to a poor quality of life, low medication adherence, progression to drug-resistant tuberculosis, and ultimately, mortality.
OBJECTIVES: This study aimed to estimate the pooled prevalence of depression in

TB patients and identify the predictors of depression in this population in India.
METHODS: The preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed for reporting this systematic review and meta-analysis. Data were extracted from October to December 2024 using the PUBMED, Scopus, EMBASE, and DOAJ databases. A total of 25 articles were selected, and the included articles underwent quality assessment using the Joanna Briggs Institute Critical Appraisal checklist. The pooled prevalence of depression in TB patients was estimated at a 95% confidence interval using a random effects model, assuming potential heterogeneity. STATA 18 (Stata Corp LLC, College Station, TX, USA) was used for analysis.
RESULTS: The total sample across 25 studies included 12,033 (Mean(SD) = 481(1377), Median = 169, IQR = 106-302). The pooled prevalence of depression in TB patients in India was estimated at 37% (95% CI: 26- 49%). A subgroup analysis based on the types of TB cases indicated that the prevalence of depression in different kinds of TB cases did not vary substantially, with 39% (95% CI: 26- 54%) in both Drug-Resistant (DR) and Drug-Sensitive (DS) Tuberculosis (TB) cases, followed by DR-TB cases [36% (95% CI: 09-68%)] and DS-TB cases [32% (95% CI: 14- 53%)]. Of the nine assessment tools used to assess depression, the pooled prevalence utilising the Patient Health Questionnaire (PHQ)-9 tool was highest [43% (95% CI: 31-56%)]. There was considerable heterogeneity (I^2 = 99.10%) observed in the random-effects model. Factors associated with depression in TB patients included gender, demographics, education, occupation, marital and relationship issues, religion, socio-economic status, habitat, disease-related factors, treatment-related factors, and social and Behavioural factors.
CONCLUSION: The study found that over one-third of TB patients experienced depression. The coexistence of depression and TB constitutes a significant public health issue that needs addressing at both the community and health facility levels.

DOI: 10.1007/s44192-025-00248-9
PMCID: PMC12255643
PMID: 40650839

Conflict of interest statement: Declarations. Ethics approval and consent to participate: Since the current study is a systematic review and meta-analysis based on published literature, no ethical approval was sought. No individual patient data was used, and all included studies were publicly available. The study was conducted following the principles of the Declaration of Helsinki and the ethical principles of publication, as established by the Committee on Publication Ethics. Consent for publication: Not applicable. Competing

interests: The authors declare no competing interests.

27.Identification and quantification of gyrA variants in fluoroquinolone-resistant Mycobacterium tuberculosis in a MeltArray reaction.

J Clin Microbiol. 2025 Jul 9;63(7):e0014625. doi: 10.1128/jcm.00146-25. Epub 2025 Jun 3.

Tu C(#)(1), Su B(#)(2), Xiong Y(1), Xia Z(1), Xiang C(1), Tan Y(2), Xu Y(1), Li Q(1).

Author information:
(1)Engineering Research Centre of Molecular Diagnostics of the Ministry of Education, State Key Laboratory of Cellular Stress Biology, State Key Laboratory of Molecular Vaccinology and Molecular Diagnostics, School of Life Sciences, Faculty of Medicine and Life Sciences, Xiamen University, Xiamen, China.
(2)Guangzhou Chest Hospital, Guangzhou, China.
(#)Contributed equally

Fluoroquinolones (FQs) resistance in Mycobacterium tuberculosis (MTB), primarily driven by mutations in the quinolone resistance-determining region (QRDR) of gyrA, poses a major concern in treating for multidrug-resistant tuberculosis (MDR-TB). These QRDR mutations are known to confer varying levels of resistance, leading to differences in treatment outcomes. Here, we introduced the MeltArray MTB/FQs assay, a multiplex PCR method that detected 11 gyrA-QRDR mutations and quantified their fractions via a polynomial regression algorithm-based formula, enabling mutation identification and quantification within 3 h in one reaction. This assay, with a limit of detection (LOD) of 50 copies/reaction, could identify mixtures containing 5% mutant gDNA across 50 to 50,000 copies/reaction. Clinical evaluation of 442 culture samples displayed 95.23% sensitivity and 99.32% specificity compared with phenotypic antimicrobial susceptibility testing (pAST). Evaluation of 121 paired sputum-culture samples revealed sensitivities of 90.32% in sputum samples and 95.24% in culture samples, both with specificities of 100%, when compared with pAST. Further evaluation of 285 sputum samples showed 93.75% positive percent agreement (PPA) and 98.10% negative percent agreement (NPA) in comparison with the MeltPro MTB/FQs kit (Zeesan Biotech, China). All mutant samples identified by MeltArray MTB/FQs but classified as susceptible by pAST or as wild type by MeltPro MTB/FQs were confirmed through Sanger sequencing and droplet digital PCR (ddPCR). The formula for predicting mutation fraction (MUT%) showed accuracy rates of 88.00%, 88.89%, and 83.33% in the training, validation, and test data sets, respectively, when compared with ddPCR results. Overall, MeltArray MTB/FQs assay offers an upgraded alternative for routine FQs resistance monitoring.IMPORTANCERising FQs

resistance has driven the spread of pre-extensively drug-resistant tuberculosis (pre-XDR-TB), challenging global tuberculosis (TB) control efforts. Conventional molecular assays for FQs resistance often cannot distinguish between low-level and high-level resistance mutations or detect low-fraction heteroresistant populations. In this study, we established a MeltArray MTB/FQs assay that can identify all the 11 critical mutations in the gyrA-QRDR with a LOD of 50 copies/reaction, enabling direct, culture-independent analysis of sputum samples. By using an algorithm to quantify mutations at levels as low as 5% in mixtures, MeltArray achieved both mutation identification and quantification within 3 h in a reaction, thus providing a powerful tool for early detection and precise management of pre-XDR-TB.

DOI: 10.1128/jcm.00146-25
PMCID: PMC12239727
PMID: 40459255 [Indexed for MEDLINE]

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

28. Patterns of compensatory mutations in rpoA/B/C genes of multidrug resistant M. tuberculosis in Uganda.

bioRxiv [Preprint]. 2025 Jul 11:2025.07.11.664293. doi: 10.1101/2025.07.11.664293.

Kateete DP, Namakula S, Kigozi E, Katabazi FA, Kasule GW, Musisi K, Wampande E, Lukoye D, Joloba ML.

Mutations in rpoB , a gene that encodes the bacterial RNA polymerase (RNAP) beta-subunit, can cause high-level resistance to rifampicin. Approximately 95% of rifampicin-resistant Mycobacterium tuberculosis clinical isolates possess mutations in an 81-base pair rpoB region referred to as the rifampicin-resistance determining region (rpoB /RRDR). Also, rifampicin-resistant M. tuberculosis clinical isolates carry multiple mutations in RNAP genes (i.e., rpoA, rpoB, rpoC, rpoD), particularly rpoA and rpoC , which encode the alpha-(α 2) and beta'-(β') subunits, respectively. Such secondary mutations offset the fitness cost associated with rifampicin-resistance mutations in M. tuberculosis , resulting in resistant strains that are as fit as the wildtype drug-susceptible strains. To analyse the patterns of compensatory mutations in RNAP encoding genes of rifampicin-resistant M. tuberculosis clinical isolates in Uganda, whole genome sequencing and Sanger DNA sequencing were performed on 52 M. tuberculosis clinical isolates - 20 drug-susceptible and 32 multidrug resistant (MDR). A total of 24 (75%) MDR-TB isolates had high-level rifampicin-resistance

conferring mutations in rpoB /RRDR i.e., Ser531Leu (31%); His526Asp (6%); His526Leu (3%); His526Tyr (3%); His526Arg (3%); His526Gly (3%); Asp516Tyr (13%); Asp516Val (6%); Glu513Lys (3%); Leu511Pro (3%); Leu492Leu (3%); Gln490Arg (3%). Further, two putative compensatory mutations (Gln490Arg & Lys1025Glu) outside the RRDR and not resistance conferring were found in rpoB . Altogether, 16 (50%) MDR-TB isolates with rpoB /RRDR resistance conferring mutations had non-synonymous mutations in rpoC of the following patterns Leu39Phe (3%); Tyr61His (3%); Asp271Gly (3%); Ser377Ala (3%); Pro481Thr (3%); Val483Ala (6%); Leu516Pro (3%); Ala521Asp (3%); Gly594Glu (13%); Asn698Ser (3%); Leu823Pro (3%). In conclusion, putative compensatory mutations are prevalent in rifampicin-resistant M. tuberculosis clinical isolates in Uganda, with rpoC /Gly594Glu and rpoC /Val483Ala as the most frequent. Further studies will determine their association with strain genetic background, fitness and transmission in an endemic setting with a high burden of HIV-TB coinfection.

DOI: 10.1101/2025.07.11.664293
PMCID: PMC12265739
PMID: 40672307

29. TB elimination in Southern Africa: overview and critical reflection.

IJTLD Open. 2025 Jul 9;2(7):381-387. doi: 10.5588/ijtldopen.25.0050. eCollection 2025 Jul.

Boffa J(1), Vambe D(2)(3), Khosa C(4)(5), José B(6), Ndjeka N(7), Nkomo T(8), Kay AW(2)(3), Mandalakas AM(2)(9), Mvusi L(7), Omar SV(10), Thi S(8), Velen K(11), Charalambous S(12)(13), Rangaka MX(14)(15).

Author information:
(1)TB Think Tank, The Aurum Institute, Johannesburg, South Africa.
(2)Global TB Program, Department of Pediatrics, Baylor College of Medicine, Houston USA.
(3)Baylor Children's Foundation Eswatini, Mbabane, Eswatini.
(4)Institute Nacional de Saúde, Marracuene, Mozambique.
(5)Department of Clinical Sciences, Liverpool School of Tropical Medicine, Liverpool, UK.
(6)National TB Control Programme, Maputo, Mozambique.
(7)TB Cluster, National Department of Health, Pretoria, South Africa.
(8)National TB Control Programme, Eswatini.
(9)Clinical Infectious Disease Group, German Center for Infection Research (DZIF), Clinical TB Unit, Research Center Borstel, Borstel, Germany.
(10)Centre for Tuberculosis, National and WHO Supranational TB Reference Laboratory, National Institute for Communicable Diseases a division of the

National Health Laboratory Service, Johannesburg, South Africa.
(11)FIND, Geneva, Switzerland.
(12)The Aurum Institute, Johannesburg, South Africa.
(13)School of Public Health, University of Witwatersrand, Johannesburg, South Africa.
(14)Institute for Global Health and MRC Clinical Trials Unit, University College London, London, United Kingdom.
(15)Wellcome Centre for Infectious Diseases Research in Africa (CIDRI-Africa), Institute of Infectious Disease & Molecular Medicine and School of Public Health, University of Cape Town, Cape Town, South Africa.

Despite significant progress, TB remains a major public health challenge in Southern Africa. We highlight the key initiatives in Eswatini, Mozambique and South Africa, which have implemented various interventions, including systematic TB screening, TB preventive treatment, targeted next-generation sequencing, targeted universal testing, and shorter drug-resistant and paediatric TB regimens. We also identify the key challenges, such as inconsistent drug access, increasing drug resistance and limited healthcare capacity, which continue to affect progress. Health systems must also balance TB care with broader healthcare priorities, and the integration of TB care into existing services requires further investment in outreach, treatment support and training. Identifying and treating missing people with TB, diagnosing TB in children, and improving treatment adherence remain critical areas requiring enhanced support and resources. While new diagnostic tools and treatments offer promise, their high costs and labour demands present barriers to routine implementation. Successful TB elimination will depend on simple, low-cost prevention, testing and treatment options, tailored to each country's specific needs. All of which will require sustained political commitment, innovation and strategic investments in health system strengthening and community-based care.

DOI: 10.5588/ijtldopen.25.0050
PMCID: PMC12248405
PMID: 40657267

30. Exploring β-lactam interactions with DacB1: unraveling optimal therapies for combating drug-resistant Mycobacterium tuberculosis.

mBio. 2025 Jul 10:e0137225. doi: 10.1128/mbio.01372-25. Online ahead of print.

Nantongo M(1)(2), Nguyen DC(3), Shin E(2)(4), Bethel CR(2), Taracila MA(2)(4), Dousa KM(4)(5), Li Q(4), Fletcher S(4), Kurz SG(6), Kreiswirth BN(7), Boom

WH(1)(4)(8), Holland S(9), Rubin EJ(10), Bonomo RA(1)(4)(5)(11).

Author information:
(1)Department of Molecular Biology and Microbiology, Case Western Reserve University (CWRU), Cleveland, Ohio, USA.
(2)Research Service, Louis Stokes Veterans Affairs Medical Center, Cleveland, Ohio, USA.
(3)Division of Infectious Diseases, Department of Pediatrics and Division of Infectious Diseases, Department of Internal Medicine, Rush University Medical Center, Chicago, Illinois, USA.
(4)Department of Medicine, CWRU, Cleveland, Ohio, USA.
(5)Medical Service, Veterans Affairs Northeast Ohio Healthcare System (VANEOHS), Cleveland, Ohio, USA.
(6)Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Yale School of Medicine, New Haven, Connecticut, USA.
(7)Center for Discovery and Innovation, Hackensack, New Jersey, USA.
(8)Division of Infectious Diseases and HIV Medicine, University Hospitals Cleveland Medical Center, Cleveland, Ohio, USA.
(9)Laboratory of Clinical Immunology and Microbiology, National Institutes of Health, National Institute of Allergy and Infectious Diseases, Bethesda, Maryland, USA.
(10)Department of Immunology and Infectious Diseases, Harvard T. H. Chan School of Public Health, Boston, Massachusetts, USA.
(11)Departments of Biochemistry, Pharmacology, and Proteomics and Bioinformatics, CWRU; Cleveland Geriatrics Research Education and Clinical Center (GRECC), VANEOHS; CWRU Cleveland VAMC Center for Antibiotic Resistance and Epidemiology (Case VA CARES), Cleveland, Ohio, USA.

Tuberculosis (TB) continues to pose a global public health threat, exacerbated by rising drug-resistant strains of Mycobacterium tuberculosis (Mtb). DacB1, a D,D-carboxypeptidase critical in Mtb peptidoglycan biosynthesis, is a promising target for β-lactam antibiotics (BLs), which remain underutilized in TB treatment. Dual BL therapy may enhance efficacy by inactivating multiple targets within the peptidoglyan synthesis pathway. Minimum inhibitory concentrations (MICs) for β-lactams and β-lactamase inhibitors against Mtb H37Ra, H37Rv, and clinical isolates showed that imipenem, meropenem, or tebipenem MICs were reduced when combined with amoxicillin or ceftriaxone or β-lactamase inhibitors such as clavulanate or durlobactam. Timed electrospray ionization mass spectrometry (ESI-MS) captured acyl-enzyme adducts between DacB1 and BLs, revealing binding interactions with carbapenems (imipenem, meropenem, and tebipenem) but not most penicillins or cephalosporins except cloxacillin and cefoxitin. Differential scanning fluorimetry (DSF) combined with circular dichroism (CD) confirmed physical and structural changes in DacB1 upon BL binding despite no alteration in melting temperature. Carbapenem-DacB1

interactions were notably faster with imipenem, likely due to reduced steric hindrance compared to meropenem and tebipenem. Molecular modeling revealed conserved penicillin-binding protein motifs within the active site of DacB1: S121XXK124, S176XN178, and K282TG284 (PDB ID # 4PPR). Building on this, molecular docking suggested favorable interactions between these motifs and the carbapenems: the carbapenem carbonyl group aids in positioning within DacB1's oxyanion hole, ready for acylation, while hydrophobic interactions with the cyclic R2 side chains and C1 methyl groups in meropenem and tebipenem contribute to steric hindrance hence slow acyl-enzyme formation. These findings enhance our understanding of DacB1 inhibition and suggest that carbapenems, particularly in combination therapies, hold promise as effective TB treatments.
IMPORTANCE: TB remains a significant public health threat, particularly due to the rising prevalence of drug-resistant Mtb strains. Current treatment options for drug-resistant TB are costly, toxic, and often ineffective, necessitating the exploration of alternative therapeutic strategies. This study is of critical importance as it investigates the potential of β-lactam antibiotics (BLs), a class historically considered ineffective against Mtb, for repurposing in TB treatment. By targeting DacB1, a key enzyme in Mtb peptidoglycan biosynthesis, this research provides new insights into the mechanism of β-lactam interactions and their potential to disrupt cell wall synthesis. The findings demonstrate that dual β-lactam therapy and β-lactam/β-lactamase inhibitor combinations enhance antibiotic efficacy, suggesting a promising avenue for combating drug-resistant TB. Furthermore, structural and molecular analyses confirm that carbapenems, particularly imipenem, meropenem, and tebipenem, effectively bind to DacB1, paving the way for optimized treatment strategies. Given the challenges in developing new TB drugs, repurposing β-lactams offers a cost-effective and readily implementable solution to address antimicrobial resistance. This study contributes valuable knowledge that could accelerate the development of novel TB therapies, improve treatment success rates, and ultimately reduce TB-related mortality worldwide.

DOI: 10.1128/mbio.01372-25
PMID: 40637416

31. High Rates of Mortality During Drug-Resistant Tuberculosis Treatment Among Individuals With Diabetes Mellitus and Low Body Mass Index.

Open Forum Infect Dis. 2025 Jun 25;12(7):ofaf344. doi: 10.1093/ofid/ofaf344. eCollection 2025 Jul.

Veeken LD(1), Kulsum ID(2), Lestari BW(1)(3)(4), Santoso P(2), Soetedjo NNM(2)(4), Koesoemadinata RC(4), Miranda AV(4), Sukmawati W(4), Salindri

AD(4)(5), Soeroto AY(2)(4), van Crevel R(1)(6).

Author information:
(1)Department of Internal Medicine and Radboud Community for Infectious Diseases, Radboud University Medical Center, Nijmegen, The Netherlands.
(2)Department of Internal Medicine, Faculty of Medicine, Hasan Sadikin General Hospital, Universitas Padjadjaran, Bandung, Indonesia.
(3)Department of Public Health, Faculty of Medicine, Universitas Padjadjaran, Bandung, Indonesia.
(4)Tuberculosis Working Group, Research Center for Care and Control of Infectious Diseases, Universitas Padjadjaran (RC3ID Unpad), Bandung, Indonesia.
(5)Division of Infectious Diseases and Geographic Medicine, Department of Medicine, Stanford University School of Medicine, Stanford, California, USA.
(6)Centre for Tropical Medicine and Global Health, Nuffield Department of Medicine, University of Oxford, Oxford, United Kingdom.

BACKGROUND: Diabetes is a risk factor for mortality during rifampicin-resistant tuberculosis (RR-TB) treatment, but whether its impact differs by nutritional status is unknown. We estimated the effect of diabetes and its interaction with low body mass index (BMI) (ie, <18.5 kg/m2) on all-cause mortality during treatment of RR-TB.
METHODS: We used medical record data of adults treated for RR-TB in Indonesia between March 2020 and May 2022. Diabetes was defined as glycated hemoglobin ≥6.5% or prior diabetes diagnosis by healthcare providers. Cox proportional hazards regression was used to estimate the hazard rates of mortality during treatment comparing those with and without diabetes. Multiplicative and additive interactions were evaluated to determine if the effect of diabetes on mortality during treatment was moderated by BMI status.
RESULTS: Among 345 individuals (57% male, 1.7% with human immunodeficiency virus, 59% with BMI <18.5 kg/m2), 96 (28%) had diabetes and 62 (18%) died. Adjusting for confounders, the hazard rates of mortality during treatment were higher among those with diabetes (adjusted hazard rate ratio [aHR], 2.05 [95% CI, 1.17-3.58]) or those with BMI <18.5 kg/m2 (aHR, 2.33 [95% CI, 1.28-4.21]). No significant multiplicative nor additive interaction was detected, but the hazard rates of mortality were highest among those with diabetes and BMI <18.5 kg/m2 (aHR, 7.14 [95% CI, 2.71-18.82]) compared to those without diabetes and BMI ≥18.5 kg/m2.
CONCLUSIONS: Having diabetes doubled the risk of mortality during RR-TB treatment. Highest mortality rates were observed among individuals with combined diabetes and low BMI.

DOI: 10.1093/ofid/ofaf344
PMCID: PMC12207741
PMID: 40599491

Conflict of interest statement: Potential conflicts of interest. All authors: No reported conflicts.

32. Spatial clusters of risk and cartography of care for drug-resistant tuberculosis.

Rev Saude Publica. 2025 Jun 30;59:e11. doi: 10.11606/s1518-8787.2025059006489. eCollection 2025.

Ballestero JGA(1), Silva Júnior JNB(1), Arroyo LH(1), Pelissari DM(2), Rigolin IZ(1), Palha PF(1), Monroe AA(1), Ferreira QR(1), Leal GDC(1), Teixeira LO(1), Costa YBD(1), Pinto IC(1), Andrade RLP(1), Arcêncio RA(1).

Author information:
(1)Universidade de São Paulo. Escola de Enfermagem de Ribeirão Preto. Ribeirão Preto, SP, Brasil.
(2)Universidade de São Paulo. Faculdade de Saúde Pública. São Paulo, SP, Brasil.

OBJECTIVE: To identify spatial clusters of risk and map the care network for people with drug-resistant tuberculosis in the state of São Paulo.
METHODS: This is an ecological study, carried out by collecting data from the Special Tuberculosis Treatment Information System (Site-TB) of people treated for drug-resistant tuberculosis from 2013 to 2020, in the state of São Paulo. Mapping was carried out using Kernel and scan statistic techniques.
RESULTS: 1,084 cases were reported in the period analyzed. São Paulo, Ribeirão Preto, Santos, Guarulhos, and Campinas were the municipalities with the highest number of cases. The spatial pattern of agglomeration of cases and referral centers for treatment were similar, with gaps in coverage in the southwest and northwest of the state. Six spatial clusters were identified: four low-risk and two high-risk, located in São Paulo, Diadema, Santos, and Guarujá.
CONCLUSIONS: The concentration of cases and tertiary referral centers in metropolitan areas highlights inequalities in access to treatment for drug-resistant tuberculosis. These findings indicate the need for health policies to expand diagnosis and treatment, improving the control of drug-resistant tuberculosis in the state of São Paulo.

OBJETIVO: Identificar aglomerados espaciais de risco e cartografar a rede de cuidado às pessoas com tuberculose drogarresistente no estado de São Paulo.
MÉTODOS: Trata-se de estudo do tipo ecológico, realizado por meio da coleta de

dados provenientes do Sistema de Informação de Tratamentos Especiais de Tuberculose (Site-TB) de pessoas tratadas para tuberculose drogarresistente de 2013 a 2020, no estado de São Paulo. Foi realizada a cartografia por meio das técnicas Kernel e de estatística de varredura.
RESULTADOS: Foram notificados 1.084 casos no período analisado. São Paulo, Ribeirão Preto, Santos, Guarulhos e Campinas foram os municípios que apresentaram o maior número de registros. O padrão espacial de aglomeração dos casos e dos Centros de Referência para o tratamento foram similares, com vazios de cobertura no sudoeste e noroeste do estado. Seis aglomerados espaciais foram identificados: quatro de baixo risco e dois de alto risco, localizados em São Paulo, Diadema, Santos e Guarujá.
CONCLUSÕES: A concentração de casos e Centro de Referência Terciária em áreas metropolitanas evidencia desigualdades no acesso ao tratamento da tuberculose drogarresistente. Estes achados indicam a necessidade de políticas de saúde para expandir o diagnóstico e tratamento, melhorando o controle da tuberculose drogarresistente no estado de São Paulo.

DOI: 10.11606/s1518-8787.2025059006489
PMCID: PMC12211794
PMID: 40608609 [Indexed for MEDLINE]

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

33. The contribution of TB rapid diagnostic testing in reducing TB-related mortality in Sub-Saharan Africa- in both Person-Living with HIV and HIV-Negative populations: A 9-year quantitative retrospective analysis.

BMC Infect Dis. 2025 Jul 21;25(1):929. doi: 10.1186/s12879-025-11310-w.

Chi FM(1)(2), Moungui HC(3)(4), Musaga NA(5), Mbatchou-Ngahane BH(6)(7).

Author information:
(1)HIV/AIDS and TB treatment units, Foumban Regional Hospital annex, West Region, Cameroon. chimcwright@gmail.com.
(2)Unicaf University of Malawi, Lilongwe, Malawi. chimcwright@gmail.com.
(3)Higher institute for Scientific and Medical Research, Yaounde, Cameroon.
(4)Faculty of Health Sciences, Open University of Catalonia, Barcelona, Spain.
(5)London School of Hygiene and Tropical Medicine, London, UK.
(6)Department of Internal Medicine, Faculty of Medicine and Pharmaceutical Sciences, University of Douala, Douala, Cameroon.
(7)Douala General Hospital, Littoral Region, Cameroon.

BACKGROUND: A potential contributor to achieving WHO's "End-TB" goal of 90% reduction in TB related mortality by 2030, is scale-up of TB Rapid Diagnostic Testing (RDT). Our study evaluated the contribution of RDTs' in reducing TB-related mortality in both PLHIV and the HIV-negative population, from 2015 to 2023 in Sub-Saharan Africa (SSA).
METHODS: We carried out an 9-year quantitative retrospective analysis of country-level data (annual WHO TB reports) for all countries in SSA reporting to the WHO. We estimated the following parameters: incidence, notification, percentage of undiagnosed TB patients, percentage diagnosis with RDTs, and TB-related mortality. We stratified the reports according to TB incidence (creating incidence strata) and limited further analysis to reports where the percentage of undiagnosed individuals was 30% or less. We then used scatter plots to examine the existence of a relationship between the use of RDTs and TB-related mortality, and quantified the observed relationships via linear regression models.
RESULTS: Over the nine years, SSA made great strides toward the 2025 milestones of End-TB disease burden-related targets; TB disease incidence decreased by 14%; TB-related mortality decreased by 27.2%; and TB/HIV-related mortality decreased by 64.1%. Similarly, RDT became the priority TB disease diagnostic modality (66.0% in 2023). We found a consistent inverse relationship between RDT scale-up and TB-related mortality in the HIV-negative population, which was significantly stronger in the higher TB incidence settings ($R2 = 0.692$, $P = 0.003$). Following adjustments ($R2 = 0.883$, $P = < 0.001$), independent predictors of TB related mortality in this population were TB RDT use, TB incidence, TB notification, percentage undiagnosed TB and percentage with drug resistant TB. In contrast, the relationship was weaker and inconsistent in the PLHIV population and was significant only where the TB incidence among PLHIV was very high ($R2 = 0.541$, $P = 0.0239$). Following adjustments ($R2 = 0.944$, $P < 0.001$), just TB incidence and TB treatment coverage in PLHIV were independent predictors of TB mortality in this population.
CONCLUSIONS: This study provides support about the anticipated contributions of RDTs in decreasing TB-related mortality in SSA, highlighting the importance of maximum scaleup (addressing underdiagnosis of TB) and limiting the biased prioritization of PLHIV for these RDTs.

DOI: 10.1186/s12879-025-11310-w
PMCID: PMC12278536
PMID: 40691764 [Indexed for MEDLINE]

Conflict of interest statement: Declarations. Ethics approval and consent to participate: Not applicable. Consent for publication: Not applicable. Competing

interests: The authors declare no competing interests.

34. Nanopore-based targeted sequencing (NTS) for drug-resistant tuberculosis: an integrated tool for personalized treatment strategies and guidance for new drug Development.

BMC Infect Dis. 2025 Jul 1;25(1):861. doi: 10.1186/s12879-025-11227-4.

Yang C(#)(1), Dai G(#)(1), Guo Y(2), Wang T(1), Gao W(#)(3), Zeng Y(#)(4).

Author information:
(1)Department of Tuberculosis, The Second Hospital of Nanjing, Nanjing, 211100, China.
(2)Department of Tuberculosis, The Second Hospital of Nanjing, The School of Public Health of Nanjing Medical University, Nanjing, 211166, China.
(3)Department of Tuberculosis, The Second Hospital of Nanjing, Nanjing, 211100, China. weiweigao1106@163.com.
(4)Department of Tuberculosis, The Second Hospital of Nanjing, Nanjing, 211100, China. 960559051@qq.com.
(#)Contributed equally

BACKGROUND: Drug-resistant tuberculosis has emerged as a major public health issue that requires immediate attention. NTS is an innovative method that allows for the direct detection of clinical samples without the need for culture. It could provide more accurate, reliable, and comprehensive information on drug resistance.
METHODS: We collected clinical data retrospectively from patients suspected of having drug-resistant tuberculosis who visited the tuberculosis department at the Second Hospital of Nanjing in Jiangsu Province, China, from December 2023 to December 2024. The diagnostic efficiency of NTS for different types of drug-resistant tuberculosis and antimicrobial resistance was calculated. The relationship between resistance genes, mutated amino acids, and mutation sites was demonstrated.
RESULTS: In this study, a total of 107 patients with drug-resistant tuberculosis were included, comprising 43 cases of mono-drug resistant tuberculosis, 20 patients with poly-drug resistant tuberculosis, 22 cases of multidrug-resistant tuberculosis, 21 cases of pre-extensively drug-resistant tuberculosis and 1 case of extensively drug-resistant tuberculosis. The accuracy of NTS in diagnosing drug-resistant tuberculosis ranged from 42.9 to 93.0%. Except for second-line injectable drugs, NTS achieved a sensitivity of over 70% for other anti-tuberculosis drugs. Serine was identified as the most frequently mutated amino acid in both the rpoB gene (66.2%, 49/74) and the katG gene (86.3%, 44/51). Additionally, the most frequently mutated amino acids in the embB gene,

rpsL gene, and gyrA gene were methionine (94.7%, 44/51), lysine (100%, 28/28), and aspartic acid (66.7%, 20/30), respectively.
CONCLUSION: NTS could effectively and precisely deliver comprehensive drug resistance results, assisting medical professionals to create more personalized treatment plans. Besides, it would encourage the development of new anti-tuberculosis drugs to broaden clinical treatment options for drug-resistant tuberculosis.

DOI: 10.1186/s12879-025-11227-4
PMCID: PMC12220424
PMID: 40596923 [Indexed for MEDLINE]

Conflict of interest statement: Declarations. Ethics approval and consent to participate: The study received approval from the Human Research Ethics and System Review Committee of the Second Hospital of Nanjing (ID: 2024-LS-ky026). The study protocol was consistent with the ethical guidelines of the 1975 Declaration of Helsinki. Consent to participate: Informed consent was obtained from all the participants. Consent for publication: Not applicable. Conflict of interest: All authors have no conflict of interest to declare. Clinical trial number: Not Applicable.

35. Comprehensive evaluation of the MeltPro MTB/PZA assay for prediction of pyrazinamide resistance in multidrug-resistant tuberculosis.

Microbiol Spectr. 2025 Jul;13(7):e0274524. doi: 10.1128/spectrum.02745-24. Epub 2025 May 22.

He G(#)(1)(2), Tu C(#)(3)(4), Zhu Y(#)(5), Zheng Q(2), Zhou Q(3)(4), Zhou W(1), Huang O(1), Chen B(5), Liu Z(5), Xu Y(3)(4), Jiang X(1).

Author information:
(1)Department of Infectious Diseases, Wenzhou Central Hospital, The Dingli Clinical College of Wenzhou Medical University, Wenzhou, China.
(2)Laboratory of Infectious Diseases, Wenzhou Central Hospital, The Dingli Clinical College of Wenzhou Medical University, Wenzhou, China.
(3)Engineering Research Centre of Molecular Diagnostics of the Ministry of Education, State Key Laboratory of Cellular Stress Biology, School of Life Sciences, Faculty of Medicine and Life Sciences, Xiamen University, Xiamen, Fujian, China.
(4)Engineering Research Centre of Molecular Diagnostics of the Ministry of

Education, State Key Laboratory of Molecular Vaccinology and Molecular Diagnostics, School of Life Sciences, Faculty of Medicine and Life Sciences, Xiamen University, Xiamen, Fujian, China.
(5)Department of Tuberculosis Control and Prevention, Zhejiang Provincial Center for Disease Control and Prevention, Hangzhou, China.
(#)Contributed equally

Resistance to pyrazinamide (PZA) poses significant challenges to tuberculosis (TB) management, and prediction of susceptibility to PZA has been challenging. This study examined PZA resistance-associated gene mutations in 125 multidrug-resistant clinical isolates of Mycobacterium tuberculosis (MTB) from Wenzhou, China. Phenotypic drug-susceptibility testing (pDST) for PZA was performed on clinical isolates using the MGIT 960 system to accurately determine resistance. Subsequently, whole-genome sequencing (WGS) was conducted on the 125 isolates to identify genetic mutations linked to PZA resistance, focusing specifically on the pncA, rpsA, and panD genes. To provide a rapid diagnostic alternative to traditional methods, the MeltPro MTB/PZA assay was also utilized to detect mutations in pncA. pDST revealed a PZA resistance rate of 59.20%, with 29.41% observed in strains resistant only to isoniazid and rifampicin, 77.61% in pre-extensively drug-resistant TB (pre-XDR-TB), and 100% in extensively drug-resistant TB (XDR-TB). Among the isolates, WGS identified mutations primarily in the pncA (64.00%) and rpsA (6.40%), with panD mutations not detected. PZA resistance was strongly associated with pncA mutations, present in 97.30% of PZA-resistant strains. WGS demonstrated 97.30% sensitivity and 84.31% specificity compared to pDST, while MeltPro MTB/PZA showed 91.89% sensitivity and 86.27% specificity. Compared to WGS, MeltPro MTB/PZA showed 92.50% positive percent agreement and 97.78% negative percentage agreement, highlighting its diagnostic value. In conclusion, PZA resistance in multidrug-resistant tuberculosis (MDR-TB) is primarily due to pncA mutations. MeltPro MTB/PZA assay offers a reliable, rapid alternative for PZA resistance prediction, supporting timely treatment adaptations for improved TB patient care.
IMPORTANCE: This study underscores the pressing need for reliable diagnostic methods to address high PZA resistance rates in TB cases, particularly in MDR-TB strains. By confirming that pncA mutations are the principal drivers of PZA resistance, we highlight the diagnostic potential of the MeltPro MTB/PZA assay as a rapid and effective alternative to conventional culture-based methods. Demonstrating sensitivity and specificity comparable to WGS and pDST, this assay offers a practical, accessible approach for timely PZA resistance prediction. It supports more tailored and effective MDR-TB treatment strategies, which are essential for optimizing patient care in both well-resourced and constrained settings.

DOI: 10.1128/spectrum.02745-24
PMCID: PMC12210976

PMID: 40401978 [Indexed for MEDLINE]

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

36. Evaluation of the role of whiB6 and kdpDE in the dominant multidrug-resistant clone Mycobacterium tuberculosis B0/W148.

Microbiol Spectr. 2025 Jul;13(7):e0322424. doi: 10.1128/spectrum.03224-24. Epub 2025 May 22.

Bonnet I(1)(2), Orgeur M(3), Brossier F(1)(2)(3), Sayes F(3), Frigui W(3), Madacki J(3), Varet H(4), Chauffour A(1)(2), Aubry A(1)(2), Veziris N(1)(2), Sougakoff W(1)(2), Brosch R(3), Tournebize R(1)(5).

Author information:
(1)Cimi-Paris, INSERM, U1135, Centre d'Immunologie et des Maladies Infectieuses, Sorbonne Université, Paris, France.
(2)Centre National de Référence des Mycobactéries et de la Résistance des Mycobactéries aux Antituberculeux, Hôpital Pitié-Salpêtrière, Assistance Publique-Hôpitaux de Paris (AP-HP), Sorbonne-Université, Paris, France.
(3)Institut Pasteur, Université Paris Cité, CNRS UMR 6047, Unit for Integrated Mycobacterial Pathogenomics, Paris, France.
(4)Institut Pasteur, Université Paris Cité, Bioinformatics and Biostatistics Hub, Paris, France.
(5)Institut Pasteur, Université Paris Cité, Photonic Bio-Imaging, Centre de Ressources et Recherches Technologiques (UTechS-PBI, C2RT), Paris, France.

Multidrug-resistant (MDR) strains of Mycobacterium tuberculosis represent an obstacle to eradicating tuberculosis (TB) due to the low treatment success rate of MDR TB. Among them, the MDR B0/W148 clone has recently evolved from the M. tuberculosis Beijing lineage 2 and is widely disseminated in Russia and Europe. To get more insights into the genetic factors underlying the evolutionary success of the MDR M. tuberculosis B0/W148 clone in addition to environmental and patient-related features, we focused on two mutations specific to this clone that are found in the transcriptional regulators WhiB6 and KdpDE and investigated in a H37Rv strain background the transcriptional profile associated with these mutations and their impact on the in vitro and in vivo growth characteristics. Through the construction and use of H37RvΔwhiB6, H37RvΔkdpDE, and complemented strains, neither mutation impaired the in vitro growth of M. tuberculosis in standard mycobacterial growth media. The mutation T51P in whiB6 prevented the upregulation of 9 genes in the esx-1 core region and 44 genes elsewhere in the genome, while the deletion of two nucleotides in kdpD leads to

a fusion protein of KdpD with KdpE that inhibits the transcriptional activity of KdpE. Neither mutation led to hypervirulence in a mouse infection model. These results point to the role of other MDR B0/W148 specific mutations in the wide geographic diffusion of this clone and/or put in question a hypothesized hypervirulence as a driving factor for this large dissemination.
IMPORTANCE: Human tuberculosis (TB), caused by the bacterium Mycobacterium tuberculosis, remains a global public health issue estimated to have been responsible for 1.25 million deaths in 2023. Multidrug-resistant (MDR) strains of M. tuberculosis, resistant to rifampicin and isoniazid, lead to lower treatment success. Among them, the MDR B0/W148 clone has widely disseminated in Russia and Europe. To get more insights into the genetic factors underlying the evolutionary success of this clone, we investigated two strain-specific mutations found in the transcriptional regulators WhiB6 and KdpDE. By constructing and analyzing laboratory M. tuberculosis strains carrying these specific mutations, we found numerous changes in their transcriptional profiles, whereas we observed only a little impact of these mutations on the virulence of M. tuberculosis in a mouse infection model. Our study provides new insights into the transcriptional landscape of the selected MDR strains, although no direct connection to virulence could be established.

DOI: 10.1128/spectrum.03224-24
PMCID: PMC12210973
PMID: 40401952 [Indexed for MEDLINE]

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

37. Sudapyridine (WX-081) inhibits Mycobacterium tuberculosis by targeting ATP synthase and upregulating host innate immunity.

mSphere. 2025 Jun 25;10(6):e0014925. doi: 10.1128/msphere.00149-25. Epub 2025 May 21.

Li X(#)(1)(2), Luo X(#)(1)(2), Wang B(1)(2), Fu L(1)(2), Chen X(1)(2), Lu Y(1)(2).

Author information:
(1)Department of Pharmacology, Beijing Chest Hospital, Capital Medical University, Beijing, China.
(2)Beijing Key Laboratory of Drug Resistance Tuberculosis Research, Beijing Tuberculosis and Thoracic Tumor Research Institute, Beijing, China.
(#)Contributed equally

Drug-resistant tuberculosis (DR-TB) urgently requires safer, more accessible

alternatives to bedaquiline (BDQ), which faces critical flaws like cardiotoxicity, high costs, and emerging resistance. WX-081, a promising BDQ alternative, has demonstrated superior anti-TB activity and improved safety in clinical studies. However, its mechanism of action remains unexplored, underscoring the need for further research to optimize its potential in advancing global TB elimination efforts. This study reveals WX-081's dual mechanisms: targeting atpE to disrupt ATP synthase and proton motive force via resistance screening, gene sequencing, and functional assays while enhancing host immunity through macrophage transcriptomics. Molecular docking confirmed atpE binding sites, and immune activation pathways (NF-κB/MAPK) were identified, positioning WX-081 as a potent, safe anti-DR-TB candidate despite unresolved mechanistic details.IMPORTANCEBedaquiline, a key drug for drug-resistant tuberculosis, is restricted by safety issues impacting its clinical utility. Its next-generation alternative, WX-081, has advanced to Phase III trials but lacks in-depth studies on its mechanism and host immune-modulatory effects, necessitating further research before broad clinical adoption.

DOI: 10.1128/msphere.00149-25
PMCID: PMC12188713
PMID: 40396746 [Indexed for MEDLINE]

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

38. Tre-DST: A new drug susceptibility test for Mycobacterium tuberculosis using solvatochromic trehalose probes.

bioRxiv [Preprint]. 2025 Jun 23:2025.06.23.661142. doi: 10.1101/2025.06.23.661142.

Schwartz LA, Brodeth AL, Susilo CT, Rodolf AA, Ivanov T, Corrales EM, Kumar SS, Kamariza M.

Tuberculosis (TB) is the most lethal cause of death from a single infectious agent. In 2024, an estimated 10 million people developed TB, nearly half a million of which were infected with drug-resistant tuberculosis (DR-TB). Early detection of infection and drug resistance is critical to controlling DR-TB as this enables rapid engagement into effective care. Currently, bacterial culture and nucleic acid testing remain the primary methods for diagnosing infection, with smear microscopy being phased out. However, these methods present significant limitations for diagnosing drug resistance such as lengthy time-to-result for phenotypic tests, as well as the need for prior knowledge of resistance mutations and prohibitive cost for molecular tests. To address this, we developed a rapid phenotypic TB drug susceptibility test, termed Tre-DST,

based on novel trehalose probes, which upon metabolic conversion emit enhanced fluorescence signal, giving them their unique ability to specifically detect live mycobacteria. We used the nonpathogenic Mycobacterium smegmatis and the virulence-attenuated Mycobacterium tuberculosis (Mtb) H37Ra or auxotrophic Mtb to demonstrate a strong correlation between cost-effective plate reader results and flow cytometry data, suggesting the fluorescence plate reader is a suitable fluorescence detector for Tre-DST. We determined that adding a one-week incubation step for Mtb allowed samples originally seeded at 10 4 CFU/mL to become detectable, over two weeks earlier than colony forming unit analysis. Importantly, we found that Tre-DST reports on drug susceptibility in a drug-agnostic manner, demonstrating loss of fluorescence with frontline TB drugs rifampicin (RIF), isoniazid (INH), and ethambutol, as well as the newer drug bedaquiline. Finally, Tre-DST distinguished RIF-and INH-resistant auxotrophs from susceptible controls and accurately reported resistance activity. Ultimately, because Tre-DST is agnostic to mechanisms of drug resistance, this assay is likely compatible with all WHO-recommended DR-TB drugs as well as any future TB drugs as a diagnostic in reference laboratories.

DOI: 10.1101/2025.06.23.661142
PMCID: PMC12262397
PMID: 40666898

39.Epidemiology and Molecular Drug-Resistance Patterns of Tuberculosis in Non-Elderly Patients in Luoyang, China, 2019-2023.

Infect Drug Resist. 2025 Jun 24;18:3087-3101. doi: 10.2147/IDR.S524300. eCollection 2025.

Wang Z(#)(1)(2), Xu L(#)(2)(3), Guo T(1), Liu J(1), Jin J(1), Zhang Q(1), Jiang T(1), Zhao Z(4), Xue Y(2).

Author information:
(1)The First Affiliated Hospital, and College of Clinical Medicine of Henan University of Science and Technology, Luoyang, Henan, People's Republic of China.
(2)School of Medical Technology and Engineering, Henan University of Science and Technology, Luoyang, Henan, People's Republic of China.
(3)Luoyang Center for Disease Control and Prevention, Luoyang, Henan, People's Republic of China.
(4)Animal Science and Technology, Henan University of Science and Technology, Luoyang, Henan, People's Republic of China.
(#)Contributed equally

PURPOSE: Existing data offer limited guidance on TB control strategies for the non-elderly population, hampering effective epidemic management. This study aimed to analyze TB transmission and molecular resistance profiles among non-elderly patients (<60 years) in Luoyang City.
PATIENTS AND METHODS: From 2019-2023, 24,706 non-duplicate sputum samples from 10 TB-designated hospitals were tested for Mycobacterium tuberculosis complex (MTBC) via IS6110-targeted real-time PCR. MTBC-positive specimens underwent multicolor melting curve analysis (MMCA) to assess resistance to isoniazid (INH), rifampin (RFP), streptomycin (SM), and ethambutol (EMB). Age-stratified analyses were performed to compare drug-resistant TB (DR-TB) prevalence between elderly and non-elderly groups, with multivariate regression identifying resistance risk factors in non-elderly patients.
RESULTS: Non-elderly individuals exhibited significantly higher TB (17.54% vs 15.26%) and DR-TB (26.82% vs 21.62%) rates than the elderly (all, $P < 0.001$). Among non-elderly patients, males, retreatment cases, main urban residents and smear-positive groups had significantly elevated MTBC detection rates. The predominant resistance patterns of multidrug-resistant tuberculosis (MDR-TB) and poly-resistant tuberculosis (PDR-TB) were MDR4 (INH + RFP + EMB + SM) and PDR2 (INH + SM), with detection rates of 5.52% (142) and 2.33% (60), respectively. MTBC positive rate peaked at 30-34 years (23.10%), while the resistance rate peaked at 35-39 years. After adjusting for the effects of smear results and diagnosis year, the multivariate regression analysis model indicated that male sex, retreatment, and the main urban area were high-risk factors for TB resistance in non-elderly cases.
CONCLUSION: The non-elderly population demonstrates a significantly higher burden of both TB detection and resistance, particularly among males, retreatment cases, and main urban patients. The emergence of complex drug resistance patterns, combined with a distinct trend of younger age at infection, highlights the critical need for targeted interventions tailored to specific epidemiological and resistance profiles of MTBC-infected populations.

DOI: 10.2147/IDR.S524300
PMCID: PMC12206893
PMID: 40590043

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

40. Burden, clinical outcomes, and characteristics of tuberculosis in migrant populations in the middle East and North African region: A systematic review and Meta-analyses.

Travel Med Infect Dis. 2025 Jul-Aug;66:102872. doi: 10.1016/j.tmaid.2025.102872. Epub 2025 Jun 27.

Maatoug T(1), Seedat F(2), Elafef E(3), Ouahchi A(1), Mtiraoui A(4), Evangelidou S(5), Mansour W(6), Requena-Méndez A(7), Zenner D(8).

Author information:
(1)University of Sousse, Faculty of Medicine of Sousse, Research Laboratory Quality of Care and Management of Maternal Health Services, LR12ES03, Sousse, Tunisia; Barcelona Institute for Global Health (ISGlobal), University of Barcelona, Barcelona, Spain; Faculty of Medicine, University of Barcelona, Barcelona, Spain.
(2)City St George's University of London, London, United Kingdom.
(3)Barcelona Institute for Global Health (ISGlobal), University of Barcelona, Barcelona, Spain; Faculty of Medicine, University of Barcelona, Barcelona, Spain; Blue Nile National Institute for Communicable Diseases, University of Gezira, Sudan.
(4)University of Sousse, Faculty of Medicine of Sousse, Research Laboratory Quality of Care and Management of Maternal Health Services, LR12ES03, Sousse, Tunisia.
(5)Barcelona Institute for Global Health (ISGlobal), University of Barcelona, Barcelona, Spain.
(6)University of Sousse, Faculty of Medicine of Sousse, Research Laboratory " Metabolic Biophysics and Applied Pharmacology" LR12ES02, Tunisia.
(7)Barcelona Institute for Global Health (ISGlobal), University of Barcelona, Barcelona, Spain; Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden; CIBERINFEC, ISCIII - CIBER de Enfermedades Infecciosas, Instituto de Salud Carlos III, Centro de Investigación Biomédica en Red de Enfermedades Infecciosas, Madrid, Spain. Electronic address: requena.mendez@ki.se.
(8)Queen Mary University London, London, United Kingdom.

INTRODUCTION: Migrants in the Middle East and North Africa (MENA) region face an increased tuberculosis (TB) risk due to socioeconomic and structural barriers. This systematic review synthesises evidence on TB burden, clinical outcomes, and epidemiological characteristics among migrants in MENA.
METHODS: We searched six electronic databases and grey literature sources for studies published between 2000 and September 2024 in any language. Eligible studies reported primary data on TB prevalence, incidence, treatment outcomes, and clinical or epidemiological features in migrants. Pooled estimates were calculated using DerSimonian & Laird's random-effects model where applicable or narratively synthesised.
RESULTS: Of the 779 records identified, we included 57 studies, comprising

95,190 TB cases and 3,532,359 migrants across 12 MENA countries. TB incidence was consistently higher in migrants than non-migrants (26.7-69.8/100,000 vs. 11.5-16.8/100,000). Migrants had lower TB-related mortality (pooled OR 0.8, 95 % CI 0.7-0.9; I2 = 2.9 %), however, treatment success rates were consistently below the WHO-recommended 90 % threshold. Migrant TB patients were younger (mean age difference: 12.8 years; 95 % CI 8.8-16.0; I2 = 86.5 %) and predominantly male (sex ratio: 1:5). Drug-resistant TB was more common among migrants, though this was not always statistically significant (multi-drug-resistant TB: pooled OR 1.2; 95 % CI 0.9-1.6; I2 = 40.2 %), while extrapulmonary TB was more prevalent among non-migrants (33.4-83.4 % vs. 16.6-72.9 %).
CONCLUSION: Migrants in MENA region experience disproportionate TB burden and poorer treatment outcomes, underscoring the need for targeted interventions. Enhanced data, especially from North Africa, is essential to support regional TB elimination aligned with World Health Organization and Sustainable Development Goals.

DOI: 10.1016/j.tmaid.2025.102872
PMID: 40582476 [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.

41. Tongue swab-based molecular diagnostics for pulmonary tuberculosis and drug resistance in adults: A prospective multicenter diagnostic accuracy study.

J Infect. 2025 Jul;91(1):106517. doi: 10.1016/j.jinf.2025.106517. Epub 2025 May 23.

Wang Y(1), Ma Z(1), Liu Z(2), Dong X(3), Shu W(4), Wei M(5), Cui J(6), Shu W(7), Li R(8), Jing W(9), Shi J(9), Wang B(8), Shen D(8), Qin C(3), Shao R(3), Wan Z(4), Wu J(4), Luo L(5), Huang L(5), Pan Y(6), Gao Y(6), Li S(10), Li L(11), Pang Y(12).

Author information:
(1)Department of Bacteriology and Immunology, Beijing Key Laboratory on Drug-Resistant Tuberculosis Research, Capital Medical University, Beijing Tuberculosis & Thoracic Tumor Research Institute, Beijing, China.
(2)Key Laboratory of Digital Technology in Medical Diagnostics of Zhejiang Province, Dian Diagnostics Group Co., Ltd., Hangzhou, China; Sir Run Run Shaw

Hospital of Zhejiang University, Hangzhou, China.
(3)Department of Respiratory and Critical Care Medicine, Infectious Disease Hospital of Heilongjiang Province, Heilongjiang, China.
(4)Department of Respiratory and Critical Care Medicine, Jiangxi Chest Hospital, Jiangxi, China.
(5)Respiratory Medicine, Guangxi Zhuang Autonomous Region Chest Hospital, Liuzhou 545000, China.
(6)Department Four of Tuberculosis Medicine, The First Affiliated Hospital, Xinxiang Medical University, Xinxiang, China.
(7)Clinical Center on Tuberculosis Control, Beijing Chest Hospital, Capital Medical University/ Beijing Tuberculosis and Thoracic Tumor Research Institute, Beijing 101149, China.
(8)Key Laboratory of Digital Technology in Medical Diagnostics of Zhejiang Province, Dian Diagnostics Group Co., Ltd., Hangzhou, China.
(9)Department of Tuberculosis, Beijing Chest Hospital, Capital Medical University/Beijing Tuberculosis & Thoracic Tumor Research Institute, China.
(10)Department of Bacteriology and Immunology, Beijing Key Laboratory on Drug-Resistant Tuberculosis Research, Capital Medical University, Beijing Tuberculosis & Thoracic Tumor Research Institute, Beijing, China. Electronic address: lss9011@126.com.
(11)Department of Bacteriology and Immunology, Beijing Key Laboratory on Drug-Resistant Tuberculosis Research, Capital Medical University, Beijing Tuberculosis & Thoracic Tumor Research Institute, Beijing, China. Electronic address: liliang69@tb123.org.
(12)Department of Bacteriology and Immunology, Beijing Key Laboratory on Drug-Resistant Tuberculosis Research, Capital Medical University, Beijing Tuberculosis & Thoracic Tumor Research Institute, Beijing, China. Electronic address: pangyupound@163.com.

BACKGROUND: Tongue swabs have emerged as a promising non-invasive alternative for TB diagnosis. This study aimed to evaluate the diagnostic performance of tongue swab-based assays for detecting Mycobacterium tuberculosis (MTB) and anti-TB drug resistance.
METHODS: We conducted a multicenter study in five TB-designated hospitals in China from May to August 2024. Tongue swabs and sputum samples were collected from 720 adults with symptoms suggestive of pulmonary TB. PCR-based tongue swab testing targeting MTB-specific sequences was evaluated against microbiological reference standards (MRS) and Xpert MTB/RIF. Tongue swab-based targeted next generation sequencing was conducted to diagnose the drug-resistant TB.
RESULTS: Tongue swab testing demonstrated high diagnostic accuracy, with a concordance rate of 95.1% (95% CI: 93.2-96.5) compared to Xpert MTB/RIF, and with a sensitivity of 88.6% (95% CI: 85.3-91.8) and specificity of 98.3% (95% CI: 97.0-99.7) compared to MRS. Tongue swabs supported the detection of drug-resistant MTB using targeted next-generation sequencing, with detection

rates of 98.66% for Ct <30, 91.53% for Ct 30-33, and 84.62% for Ct 33-34, declining sharply to 57.14% for Ct 34-35.
CONCLUSION: PCR-based tongue swab testing offers a rapid, non-invasive alternative for TB diagnosis with high accuracy, particularly in paucibacillary cases or individuals unable to provide sputum. Although all participants in this study were able to provide sputum, tongue swabs may offer an alternative in situations where sputum collection is challenging. Further optimization of sampling and molecular techniques is essential to improve reliability and support broader implementation. Integrating tongue swab diagnostics with existing TB control programs could enhance the detection accuracy, improve drug resistance monitoring and reduce transmissions.

DOI: 10.1016/j.jinf.2025.106517
PMID: 40414567 [Indexed for MEDLINE]

Conflict of interest statement: Declaration of Competing Interest The materials, reagents, and instruments used in this study were provided by Hangzhou DIAN Medical Laboratory Center Co., Ltd. The authors have no financial interests or conflicts of interest with any organization or entity, except for those related to the topics or materials discussed in the manuscript. 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.

42. Lack of weight gain and increased mortality during and after treatment among adults with drug-resistant tuberculosis: a retrospective cohort study in Georgia, 2009-2020.

ERJ Open Res. 2025 Jun 23;11(3):00839-2024. doi: 10.1183/23120541.00839-2024. eCollection 2025 May.

Chakhaia T(1)(2), Blumberg HM(3), Kempker RR(3), Luo R(1), Dzidzikashvili N(2), Chincharauli M(2), Tukvadze N(2)(4), Avaliani Z(2), Stauber C(1), Magee MJ(3).

Author information:
(1)Georgia State University, Atlanta, GA, USA.
(2)National Center for Tuberculosis and Lung Disease, Tbilisi, Georgia.
(3)Emory University, Atlanta, GA, USA.
(4)Swiss Tropical and Public Health Institute, Allschwil, Switzerland.

Update of
medRxiv. 2024 Aug 06:2024.08.05.24311499. doi: 10.1101/2024.08.05.24311499.

BACKGROUND: While low body mass index (BMI) is associated with poor tuberculosis (TB) treatment outcomes, the impact of weight gain during TB treatment is unclear. To address this knowledge gap, we assessed whether a lack of weight gain is associated with all-cause mortality during and after TB treatment.
METHODS: We conducted a retrospective cohort study among adults with newly diagnosed multidrug or extensively drug-resistant (MDR/XDR) pulmonary TB in Georgia between 2009-2020. The exposure was a change in BMI during the first 3-6 months of TB treatment. All-cause mortality during and after TB treatment was assessed using the National Death Registry. We used competing-risk Cox proportional hazard models to estimate adjusted hazard ratios (aHRs) between BMI change and all-cause mortality.
RESULTS: Among 720 adult participants, 21% had low BMI (<18.5 kg·m-2) at treatment initiation and 9% died either during (n=16) or after treatment (n=50). During the first 3-6 months of TB treatment, 17% lost weight and 14% had no weight change. Among 479 adults with normal baseline BMI (≥18.5-<25 kg·m-2), weight loss was associated with an increased risk of death during TB treatment (aHR 5.25, 95% CI 1.31-21.10). Among 149 adults with a low baseline BMI, no change in BMI was associated with increased post-TB treatment mortality (aHR 4.99, 95% CI 1.25-19.94).
CONCLUSIONS: Weight loss during TB treatment (among those with normal baseline BMI) or no weight gain (among those with low baseline BMI) was associated with increased rates of all-cause mortality. Our findings suggest that scaling up weight management interventions among those with M/XDR TB may be beneficial.

DOI: 10.1183/23120541.00839-2024
PMCID: PMC12183741
PMID: 40551793

Conflict of interest statement: Conflict of interest: The authors have nothing to disclose.

43.Antimycobacterial activity of the plectasin derivative NZ2114.

Front Microbiol. 2025 Jun 26;16:1613241. doi: 10.3389/fmicb.2025.1613241. eCollection 2025.

Davids C(1), Rao-Fransson K(1), Krishnan N(2), Tenland E(1)(3), Mörgelin M(4), Robertson B(2), Godaly G(1).

Author information:

(1)Department of Microbiology, Immunology and Glycobiology, Institution of Laboratory Medicine, Lund University, Lund, Sweden.
(2)Centre for Bacterial Resistance Biology, Department of Infectious Disease, Imperial College London, London, United Kingdom.
(3)Department of Clinical Immunology and Transfusion Medicine, Skåne University Hospital, Lund, Sweden.
(4)Colzyx AB, Lund, Sweden.

INTRODUCTION: Mycobacteria have a unique hydrophobic membrane with several lipid-enriched layers that are low in permeability, setting them apart from other bacteria. This complex structure, consisting of three distinct layers is crucial for cell growth, virulence, and providing a barrier to antibiotics. Previously, we identified a plectasin variant, NZX, which showed activity against Mycobacterium tuberculosis in several murine tuberculosis (TB) infection studies. In this study, we investigated another plectasin variant, NZ2114, known for its effectiveness against Gram-positive bacteria, as a potential antimycobacterial peptide both in vitro and in vivo.
METHODS: The resazurin microtiter assay (REMA) was used to determine MIC; a time-kill assay was performed to evaluate long-term effects; scanning electron microscopy (SEM) was employed to visualize peptide impact; a checkerboard assay assessed drug compatibility; MTT and WST-8 assays were used to estimate peptide toxicity; intracellular killing was evaluated using primary macrophages; peptide stability was assessed in human serum; and a murine tuberculosis (TB) infection model was used to verify the peptide's efficacy.
RESULTS: NZ2114 effectively killed mycobacteria at a minimal inhibitory concentration (MIC99) of 6.1 μM, was non-toxic to primary human cells, and remained resistant to serum degradation while preserving its antimycobacterial capacity. In a checkerboard assay, NZ2114 demonstrated synergy with the first-line TB drugs isoniazid and ethambutol. The antimicrobial effect was also observed against several clinical isolates of Gram-positive bacteria, including Enterococcus faecalis, Enterococcus faecium, and Methicillin-Resistant Staphylococcus aureus (MRSA). In our murine TB infection model, compared to untreated controls, NZ2114 eliminated M. tuberculosis with a log reduction of 0.72 (81.14%) after three doses.
DISCUSSION: These studies suggest NZ2114 as a potential TB therapy, aiding in the control of this significant infectious disease.

DOI: 10.3389/fmicb.2025.1613241
PMCID: PMC12241124
PMID: 40641884

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

44. Bedaquiline, delamanid, linezolid, and clofazimine for rifampicin-resistant and fluoroquinolone-resistant tuberculosis (endTB-Q): an open-label, multicentre, stratified, non-inferiority, randomised, controlled, phase 3 trial.

Lancet Respir Med. 2025 Jul 16:S2213-2600(25)00194-8. doi: 10.1016/S2213-2600(25)00194-8. Online ahead of print.

Guglielmetti L(1), Khan U(2), Velásquez GE(3), Gouillou M(4), Ali MH(5), Amjad S(5), Kamal F(5), Abubakirov A(6), Ardizzoni E(7), Baudin E(4), Bektassov S(6), Berry C(8), Bonnet M(9), Chavan V(10), Coutisson S(11), Dakenova Z(12), de Jong BC(7), Dinh LV(13), Ferlazzo G(11), Kirakosyan O(14), Lachenal N(11), Lecca L(15), McIlleron H(16), Mikanda KK(17), Mucching-Toscano S(18), Mulders W(7), Mushtaque H(19), Nahid P(20), Nguyen DV(21), Nguyen NV(13), Oyewusi L(17), Motta I(22), Panda S(23), Patil S(24), Pham TH(21), Phan DT(25), Phan HTT(26), Phillips PPJ(20), Ruiz J(18), Rupasinghe P(7), Salahuddin N(19), Sanchez-Garavito E(27), Seung KJ(28), Asfaw MT(17), Vargas Vasquez D(29), Rich ML(30), Varaine F(31), Mitnick CD(32); endTB-Q Clinical Trial Team.

Collaborators: Arora G, Ashara V, Bhattacharjee S, Borkar R, Chincholikar N, Choudhary N, Davuluri P, Desai N, Dipika, Dhongade S, Dulani D, Ghule S, Hirani N, Hurali P, Irani R, Jadhav K, Jadhav P, Jadhav R, Joseph N, Joshi A, Joshi P, K A, K S, Kamble M, Kate R, Keer T, S Kenche M, Khandare H, Koli P, Kulkarni A, Patra SK, Kuwar A, Lande P, Mane N, Masalge P, Mishra P, Mitkari R, More A, Munot P, Murgesh R, Muthe S, Nakashe N, Natarajan D, Paril S, Patil S, Patil V, Patwardhan V, Posture V, Pradeshi A, Prasad V, Pundir B, Rajendran S, Randhit Y, Rekart M, Samant P, Shaikh H, Sharma A, Sharma N, Sharma S, Shinde N, Shinde S, Shingare G, Shulka A, Shriwas A, Sonawane L, Sudhindra U, Suryavanshi D, Thakare A, Udare D, Vaidya G, Wagh R, Isenova L, Konigratbayeva G, Nurtayeva G, Zekeshov N, Chenu R, Garba S, Tozzi D, Yuya-Septoh FJ, Thi Tuyet Mai B, Thi Hai D, Thi Thuy D, Thi Oanh L, Do BT, Nguyen DT, Nguyen PH, Nguyen TMA, Nguyen TTH, Nguyen TKN, Nguyen TN, Nguyen VK, Nog N, Pham TN, Pham TL, Pham TA, Phung TB, Tran BT, Trinh MT, Chang E, Coit J, Do JM, LaHood A, O'Brien K, Okunbor E, Osso E, Chávez V, Larco P, Mendoza D, Robles C, Rojas A, Salazar J, Santos G, Sosa J, Ticona C, Carranza S, Delgado D, Galarza C, Murga G, Ramos E, Cantaro K, Huerta A, Maldonado J, Nuñez R, Panduro K, Rafael R, Abdul A, Abedin S, Afreen E, Ahmed S, Ahmed U, Ali Shah J, Ashraf A, Aslam F, Bashir Z, Fayyaz S, Hafeez K, Hamid M, Hassan B, Hussain M, Irfan M, Omar M, Parveen S, Sunail S, Farooq M, Mazhar B, Munir S, Sonia N, Yaseen M, Zubair M, Zehra F, Zulfiqar I, Abbasi T, Akbar Abro G, Ahmed M, Ahmed N, Hammad Ali M, Ali N, Danish R, Farhat A, Gill S, Hafeez M,

Hussain G, Inayat H, Johnson S, Kamal F, Kamran A, Kumar S, Maheshwari M, Mamsa S, Massey S, Mehmood A, Memon A, Ali Mirani A, Naz S, Rafique Qureshi T, Roop Moazzam Sheikh Y, Rafi Siddiqui M, Singh B, Soomro M, Ardizzoni E, Rigouts L, Rupasinghe P, Aftab A, Ahmed S, Adnan Alamgir M, Ali A, Ali A, Ahmed Ali S, Ali S, Altaf S, Amjad S, Sahiba Arshad M, Ausim S, Basit A, Ezik H, Hussain H, Hyder S, Inayat S, Janmohammed A, Jaseem K, Jawed A, Maniar L, Kumar P, Kumar S, Latif R, Liaqat S, Ammar Nasser M, Shakeel M, Shaikh S, Siddiqui A, Singh J, Sivan K, Taimoor M, Zia N, Li I, Otepbergenova M, Dinh TH, Do TT, Do TT, Le TN, Nguyen KC, Nguyen TT, Nguyen VH, Abildayeva G, Maryash O, Telegina E, Tursynbekova L, Amanzholova Z, Bektassova P, Belgozhanova A, Birimkulova N, Dyusebayeva N, Erkut N, Gusmanov A, Kassenova B, Kassym A, Khazhidinov K, Lee T, Magzumova A, Mussabayeva M, Omarova G, Ryapolova N, Sagyndykova L, Serekbay A, Stambekova A, Tanatarova G, Uaisov Z, Zhantuarova Z, Zhumakairova G, Arlyapova N, Bogus J, Cain M, Carmona M, Flanagan C, McAnaw S, Scharff A, Soni S, Striplin M, Abebe S, Alakaye J, Bulane A, Custodio M, Hajison P, Hetsa M, Holtzman D, Khesa M, Lethola M, Lebitsa T, Mahamo M, Makaka J, Matoko M, Mpinda S, Mohoang P, Monyaesa D, Nkundayirazo P, Ntsane Sesomo Mohale M, Ntsibane S, Phate S, Radebe Retsepile Tlali M, Rakhetsi M, Ranoosi T, Tamirat M, Thokoana M, Alegre E, Aguilar C, Armuto L, Barreda N, Barreto M, Cabrera S, Calderon R, Castro M, Chavez J, Chavez L, Cheje H, Cori L, Dávalos D, de la Gala S, Delgadillo K, Diaz H, Flores X, Galarza J, García D, Garcia F, Gaspar M, Godos R, Gomez P, Gonzales L, Guerrero L, Inga S, Jasaycucho J, Martel B, Pro Martinez A, Molina R, Mugruza R, Mundaca H, Nuahan M, Ore K, Panduro L, Peña O, Perea S, Pinedo C, Ponce Y, Quinte C, Quiñones M, Ramos A, Ramirez E, Reynoso R, Reyes C, Reyes J, Riccio V, Robles B, Rojas K, Sanabria O, Saravia M, Saravia S, Senador L, Soberon J, Soncco E, Soto M, Suarez C, Suarez M, Suarez V, Torpoco E, Torres O, Torrez C, Tunque G, Ugarte A, Vaderrama G, Valdivia W, Valdivia Y, Valverde I, Vargas C, Vargas J, Vasquez E, Veliz J, Villa D, Villafuerte S, Villar G, Villegas S, Wong M, Yataco R, Pham H, Truong H, Nguyen H, Huy V, Nguyen VS, Nguyen TMK, Minh T, Bui DTT, Truong VV, Nguyen TTH, Coutisson S, Atger M, Nadia Baya S, Bekhiet M, Boissière V, Caboclo R, Chaudhry M, Cloez S, Collin S, Delifer C, Demaisons S, Ducher V, Hewison C, Ibrahim M, Lebeau K, Mazmanian M, Mirzayeva R, Moreau M, Moschioni M, Pâquet A, Perrin C, Pichon L, Roussel J, Scotton M, Austin A, Sun P.

Author information:
(1)Médecins Sans Frontières, Paris, France; Department of Infectious, Tropical Diseases and Microbiology, IRCCS Sacro Cuore Don Calabria Hospital, Verona, Italy. Electronic address: lorenzo.guglielmetti@paris.msf.org.
(2)Interactive Research and Development Global, Singapore; Department of Epidemiology, Biostatistics, and Occupational Health, McGill University Montreal, Montreal, QC, Canada.
(3)Center for Tuberculosis, Institute for Global Health Sciences, University of California, San Francisco, CA, USA; Division of HIV, Infectious Diseases, and

Global Medicine, University of California, San Francisco, CA, USA.
(4)Epicentre, Paris, France.
(5)Interactive Research and Development, Karachi, Pakistan.
(6)National Scientific Center of Phthisiopulmonology, Almaty, Kazakhstan.
(7)Department of Biomedical Sciences, Institute of Tropical Medicine, Antwerp, Belgium.
(8)Médecins Sans Frontières, London, UK.
(9)Translational Research on HIV and Endemic and Emerging Infectious Diseases, Montpellier Université de Montpellier, Institut de Recherche pour le Développement, INSERM, Montpellier, France.
(10)Médecins Sans Frontières, Mumbai, India.
(11)Médecins Sans Frontières, Geneva, Switzerland.
(12)City Center of Phthisiopulmonology, Astana, Kazakhstan.
(13)National Lung Hospital, Hanoi, Viet Nam.
(14)Department of Clinical Infectious Diseases, Research Center Borstel, Leibniz Lung Center, Borstel, Germany.
(15)Socios en Salud-Sucursal, San Isidro, Peru; Global Health and Social Medicine, Harvard Medical School, Boston, MA, USA.
(16)Department of Medicine, University of Cape Town, Cape Town, South Africa.
(17)Partners In Health Lesotho, Maseru, Lesotho.
(18)Socios en Salud-Sucursal, San Isidro, Peru.
(19)The Indus Hospital and Health Network, Karachi, Pakistan.
(20)Center for Tuberculosis, Institute for Global Health Sciences, University of California, San Francisco, CA, USA.
(21)Hanoi Lung Hospital, Hanoi, Viet Nam.
(22)MRC Clinical Trials Unit, UCL, London, UK; Médecins Sans Frontières, Geneva, Switzerland.
(23)Indian Council of Medical Research, New Delhi, India.
(24)National AIDS Research Institute, Pune, India.
(25)Pham Ngoc Thach Hospital, Ho Chi Minh City, Viet Nam.
(26)Center for Tuberculosis, Institute for Global Health Sciences, University of California, San Francisco, CA, USA; Hanoi Lung Hospital, Hanoi, Viet Nam; Vietnam National TB Program University of California San Francisco Research Collaboration Unit, Center for Promotion of Advancement of Society Hanoi, Hanoi, Viet Nam.
(27)Socios en Salud-Sucursal, San Isidro, Peru; Hospital Nacional Sergio E Bernales, Comas, Peru.
(28)Division of Global Health Equity, Brigham and Women's Hospital, MA, USA.
(29)Hospital Nacional Hipólito Unanue, El Agustino, Peru; Socios en Salud-Sucursal, San Isidro, Peru.
(30)Partners In Health, Boston, MA, USA; Division of Global Health Equity, Brigham and Women's Hospital, MA, USA.
(31)Médecins Sans Frontières, Paris, France.
(32)Partners In Health, Boston, MA, USA; Division of Global Health Equity,

Brigham and Women's Hospital, MA, USA; Global Health and Social Medicine, Harvard Medical School, Boston, MA, USA.

BACKGROUND: Pre-extensively drug-resistant (pre-XDR) tuberculosis (ie, multidrug-resistant or rifampicin-resistant with additional resistance to any fluoroquinolone) is difficult to treat. endTB-Q aimed to evaluate the efficacy and safety of bedaquiline, delamanid, linezolid, and clofazimine (BDLC) compared with the standard of care for patients with pre-XDR tuberculosis.
METHODS: This open-label, multicentre, stratified, non-inferiority, randomised, controlled, phase 3 trial was conducted in ten hospitals in India, Kazakhstan, Lesotho, Pakistan, Peru, and Viet Nam. Participants aged 15 years or older who had pulmonary tuberculosis with resistance to rifampicin and fluoroquinolones were included. Participants were randomly assigned (2:1) to the BDLC group (all-oral bedaquiline 400 mg once per day for 2 weeks followed by 200 mg three times per week, delamanid 100 mg twice per day, linezolid 600 mg once per day for 16 weeks and then either 300 mg once per day or 600 mg three times per week, and clofazimine 100 mg once per day) or the control group (individualised WHO-recommended longer standard of care). Randomisation was stratified by country and baseline disease extent. BDLC was administered for 39 weeks (9-month regimen) for extensive disease and 24 weeks (6-month regimen) for limited disease and extended to 9 months for those with a positive culture at 8 weeks or later or a missing 8-week culture result. Site staff and participants were not masked, whereas investigators and laboratory staff were masked to treatment assignment. The primary endpoint was favourable outcome (two consecutive, negative cultures including one between weeks 65 and 73; or favourable bacteriological, radiological, and clinical evolution) at week 73 after randomisation in the modified intention-to-treat (mITT) and per-protocol populations. We report the risk differences adjusted for stratification variables, with a non-inferiority margin of -12%. This trial is registered with ClinicalTrials.gov, NCT03896685.
FINDINGS: Between April 4, 2020, and March 28, 2023, 1030 individuals were screened and 324 (31%) were randomly assigned (219 to the BDLC group and 105 to the control group). 114 (46%) participants were female and 133 (54%) were male. Median age was 30·5 years (IQR 21·6-43·0). 157 (64%) participants had extensive disease at baseline. In the BDLC group, 47 (29%) of 163 were assigned to receive the 6-month regimen and 116 (71%) the 9-month regimen. The core regimen of BDLC plus one or more other drugs was used for 76 (91%) of 84 participants in the control group. At week 73, favourable outcome was reached by 141 (87%) participants in the BDLC group versus 75 (89%) in the control group in the mITT population (adjusted risk difference 0·2% [95% CI -9·1 to 9·5]; pnon-inferiority=0·0051) and by 138 (88%) of 157 versus 71 (93%) of 76 in the per-protocol population (adjusted risk difference -3·5% [-12·8 to 5·9]; pnon-inferiority=0·037). Overall non-inferiority was not shown. 145 (68%) of 213 participants in the BDLC group and 77 (73%) of 105 in the control group had at

least one grade 3 or higher adverse event, with eight (4%) and two (2%) all-cause deaths by week 73, respectively.
INTERPRETATION: The shortened BDLC strategy was not non-inferior to the control. Accumulating evidence suggests that this patient population might require longer, reinforced regimens.
FUNDING: Unitaid, Médecins Sans Frontières, Partners In Health, Interactive Research and Development, Ramón Areces Foundation, the Jung Foundation for Science and Research, Research Foundation-Flanders.
TRANSLATIONS: For the Hindi, Marathi, Spanish, Vietnamese, Russian, Urdu and French translations of the abstract see Supplementary Materials section.

DOI: 10.1016/S2213-2600(25)00194-8
PMID: 40683298

Conflict of interest statement: Declaration of interests SC and NL received support from Unitaid. HM was awarded a Fellowship to the University of Cape Town from the Wellcome Trust. IM received consulting fees from the Médecins Sans Frontières (MSF) Access Campaign as an APH consultant. PPJP received funding from Partners in Health (PIH) for this study. MLR was the coleader on the endTB grant from Unitaid; received cofunding for the endTB-Q clinical trial by MSF; is provided 20% full-time employee equivalent in 2024 and 2025 from PIH for working on Global TB issues, including writing this manuscript and other manuscripts; is a technical project lead for arcTB (possible Unitaid grant at 50% full-time employee equivalent from 2025 to 2027); is a senior global health physician (average 20% full-time employee equivalent in the past 3 years); is the coinvestigator on the STEM-TB grant (average 5% full-time employee equivalent); received a career development grant in nutrition and TB from Brigham and Women's Hospital, a USAID Regional Approaches for Eradicating Tuberculosis in Central Asia grant (10% for 3 years starting Oct 1, 2024), and a grant from USAID Global Resilience Against Drug-Resistant Tuberculosis (expected to average 40% in 5 years starting Oct 1, 2024); provided consulting for WHO EURO (an observational study of modified short MDR-TB regimens in Europe and Central Asia); received travel support from WHO for a 3-day meeting on MDR-TB regimens and treatment in 2023; travel and accommodation support from Unitaid for TB meetings related to the World Union TB conference 2023; travel support for presenting the endTB trial to Unitaid and WHO in August, 2023; travel support for an endTB investigators meeting in September, 2023; and travel and accommodation support to attend the World Union TB conference in 2024. GEV received payments to his institution from Unitaid, MSF, PIH (SPHQ15-LOA-045), National Institutes of Health National Institute of Allergy and Infectious Diseases (NIH NIAID; K08

AI141740); received grants or contracts from NIH NIAID (R01 AI135124, R25 AI147375, R34 AI179568, U01 AI152980, UM1 AI068636, and UM1 AI179699); USAID (7200AA22CA00005); and received consulting fees from the Gates Medical Research Institute. All other authors declare no competing interests. DVN, LVD, and HTTP received funding to their institution from PIH for this study. BCdJ received grants from Janssen Pharmaceuticals for the C211 trial on bedaquiline for pediatric TB and for the BE-PEOPLE trial on leprosy post-exposure prophylaxis; and received grants to their institution from the Research Foundation Flanders (FWO; number FWO G0A7720N and FWO W001822N). CDM received a grant to their institution from Unitaid. CB was an MSF employee from 2015 to 2023. LG received a grant from Unitaid for the endTB project.

45. Optimising TB investments in Belarus, Moldova, Kyrgyz Republic, Tajikistan and Uzbekistan: An allocative efficiency analysis.

PLOS Glob Public Health. 2025 Jul 11;5(7):e0004548. doi: 10.1371/journal.pgph.0004548. eCollection 2025.

Bowring AL(1), Martin-Hughes R(1), Ten Brink D(1), Burke K(1), Nidzvetska S(2), Wulan N(1), Luong P(1), Perez-Bennetts E(1), Scott N(1).

Author information:
(1)Burnet Institute, Melbourne, Australia.
(2)Global Fund, Geneva, Switzerland.

High rates of drug-resistant tuberculosis (TB) are a barrier to achieving End TB-strategy targets in Eastern Europe and Central Asia. This analysis collates results from five country-level modelling studies to identify priorities to reduce TB burden. Allocative efficiency studies were conducted in 2023 in Belarus, Kyrgyz Republic, Moldova, Tajikistan and Uzbekistan using the Optima TB model to determine the optimised distribution of funds to maximise health outcomes with given resources. A baseline scenario of continued 2022 spending was compared to scenarios with spending optimised across prevention, screening and treatment interventions to reduce TB incidence and deaths over 2024-2030. Modelled pulmonary TB incidence ranged from 25-119 per 100,000 population, and 14 - 43% of new/relapse TB cases were drug resistant. In all countries, optimizing current spending involved: expanding shorter treatment regimens (6-9 months) for drug-resistant-TB over standard regimens (18-20 months); reducing mass screening and mandatory testing and expanding community-based active case finding focused among populations at higher TB risk; and scaling-up TB preventive treatment. It was recommended to expand contact tracing in three countries and to improve cost-effectiveness in two countries by focusing on child household contacts first. With current spending optimised, pulmonary TB

incidence was projected to decrease to 19 - 95 per 100,000 population by 2030, averting 1 - 13% of new/relapse TB cases and 1 - 18% of TB-related deaths from 2024-2030 compared to continued baseline spending. In three countries, optimised allocation of 150% of current spending had minimal additional epidemic impact. There are opportunities to reallocate TB funds more cost-effectively in Eastern Europe and Central Asia, but End TB targets may remain out of reach without new and prospective interventions.

DOI: 10.1371/journal.pgph.0004548
PMCID: PMC12250568
PMID: 40644395

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

46. Novel Quinazolinones Active against Multidrug-Resistant Mycobacterium Tuberculosis: Synthesis, Antimicrobial Evaluation, and in Silico Exploration of Penicillin-Binding Protein 1A as a Potential Target.

ChemMedChem. 2025 Jul 1;20(13):e202500147. doi: 10.1002/cmdc.202500147. Epub 2025 Jun 8.

Kerda M(1), Nawrot D(1), Šlechta P(1), Domanský M(1), Askari A(1), Kamangar H(1), Janďourek O(1), Konečná K(1), Paterová P(2), Hlbočanová I(1), Macháček M(1), Mori M(3), Meneghetti F(3), Doležal M(1), Zitko J(1), Bouz G(1).

Author information:
(1)Faculty of Pharmacy in Hradec Králové, Charles University, 500 05, Hradec Králové, Czech Republic.
(2)Department of Clinical Microbiology, University Hospital Hradec Králové, 500 05, Hradec Králové, Czech Republic.
(3)Department of Pharmaceutical Sciences, Università degli Studi di Milano, 20133, Milano, Italy.

Quinazolinone derivatives have emerged as promising scaffolds in antimicrobial drug discovery. This work focuses on the design, synthesis, and evaluation of novel quinazolinone-based compounds and predicts their potential to interact with mycobacterial penicillin-binding proteins (PBPs). Relying on established

structure-activity relationships of antibacterial quinazolinones, a total of 53 compounds belonging to three different structural types are synthesized and biologically evaluated for antimycobacterial, antibacterial, and antifungal activities. Biological evaluations reveal selective efficacy against Mycobacterium tuberculosis with minimum inhibitory concentrations (MICs) as low as 6.25 μg mL-1 for some derivatives, and this activity is preserved against drug-resistant strains. Molecular docking studies suggest a potential allosteric binding site in mycobacterial PBP 1A (PonA1, UniProt ID: P71707), and subsequential molecular dynamics confirm stable binding with key stabilizing interaction between the carbonyl oxygen of the quinazolinone and either ARG399 or ASP474. These findings suggest quinazolinone derivatives as viable candidates for further development as non-β-lactam PBP inhibitors, addressing the urgent need for new antitubercular therapies.

DOI: 10.1002/cmdc.202500147
PMCID: PMC12221116
PMID: 40237183 [Indexed for MEDLINE]

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

47.Coexistence of Tuberculosis and Lophomoniasis in a Patient With Alzheimer's Disease.

Respirol Case Rep. 2025 Jun 25;13(6):e70248. doi: 10.1002/rcr2.70248. eCollection 2025 Jun.

Maboudi M(1), Soleymani E(2)(3), Banimostafavi ES(4), Kordi S(1), Adelani M(5), Zakariaei Z(6), Fakhar M(2)(7)(8).

Author information:
(1)Department of Infectious Diseases, Faculty of Medicine, Antimicrobial Resistance Research Center Mazandaran University of Medical Sciences Sari Iran.
(2)Toxoplasmosis Research Center, Communicable Diseases Institute, Department of Parasitology Mazandaran University of Medical Sciences Sari Iran.
(3)Department of Parasitology and Mycology, Faculty of Medicine Mazandaran University of Medical Sciences Sari Iran.
(4)Department of Radiology Shahid Beheshti Hospital, Qom University of Medical Sciences Qom Iran.
(5)Department of Internal Ward, Pulmonary and Critical Care Division Mazandaran University of Medical Sciences Sari Iran.
(6)Department of Forensic Medicine and Toxicology, Mazandaran Registry Center

for Opioids Poisoning, Orthopedic Research Centers Imam Khomeini Hospital, Mazandaran University of Medical Sciences Sari Iran.
(7)Iranian National Registry Centre for Lophomoniasis and Toxoplasmosis, Imam Khomeini Hospital Mazandaran University of Medical Sciences Sari Iran.
(8)Department of Medical Microbiology and Immunology, School of Medicine Qom University of Medical Sciences Qom Iran.

The coexistence of lophomoniasis and tuberculosis (TB), both airborne diseases, is relatively uncommon. Co-infections like these can complicate treatment strategies due to overlapping symptoms and potential drug interactions. We report a rare case of comorbidity involving two pulmonary diseases, lophomoniasis and TB, in an 82-year-old woman with Alzheimer's disease (AD) from northern Iran. Her primary symptoms included weakness, lethargy, dyspnea, sputum production, night sweats, and significant weight loss. Both TB and lophomoniasis can compromise the immune system, potentially worsening the progression or severity of AD by increasing susceptibility to infections or enhancing neuroinflammation. Following the prescription of appropriate drug regimens for both diseases, the patient was discharged from the hospital in stable condition. Overall, it is crucial to consider lophomoniasis in the differential diagnosis of patients with pulmonary tuberculosis, especially in endemic areas where both infections are prevalent, to ensure timely diagnosis and effective management.

DOI: 10.1002/rcr2.70248
PMCID: PMC12188102
PMID: 40568182

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

48. Conflation of prediction and causality in the TB literature.

IJTLD Open. 2025 Jul 9;2(7):388-396. doi: 10.5588/ijtldopen.25.0142. eCollection 2025 Jul.

Romo ML(1), Barcellini L(2), Franke MF(1), Khan PY(3)(4).

Author information:
(1)Department of Global Health and Social Medicine, Harvard Medical School, Boston, Massachusetts, USA.
(2)Department of Pediatrics, "V. Buzzi" Children's Hospital, ASST FBF Sacco, Milan, Italy.

(3)Clinical Research Department, Faculty of Infectious and Tropical Diseases, London School of Hygiene & Tropical Medicine, London, UK.
(4)Interactive Research & Development (IRD) Global, Singapore, Singapore.

BACKGROUND: Observational data can answer both predictive and etiologic research questions; however, the model-building approach and interpretation of results differ based on the research goal (i.e., prediction versus causal inference). Conflation occurs when aspects of the methodology and/or interpretation that are unique to prediction or etiology are combined or confused, potentially leading to biased results and erroneous conclusions.
METHODS: We conducted a rapid review using MEDLINE (2018-2023) of a subset of the observational TB literature: cohort studies among people with drug-resistant TB that considered HIV status an exposure of interest and reported on TB treatment outcomes. For each article, we assessed the research question, statistical approach, presentation of results, and discussion and interpretation of results.
RESULTS: Among the 40 articles included, 32 (80%) had evidence of conflation. The most common specific types of conflation were recommending or proposing interventions to modify exposures in a predictive study and having a causal interpretation of predictors, with both types frequently co-occurring.
CONCLUSION: Conflation between prediction and etiology was common, highlighting the importance of increasing awareness about it and its potential consequences. We propose simple steps on how TB and lung health researchers can avoid conflation, beginning with clearly defining the research question.

DOI: 10.5588/ijtldopen.25.0142
PMCID: PMC12248412
PMID: 40657268

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

49. Trends in Drug Resistance and Epidemiological Patterns of Tuberculosis in Elderly Patients in Wenzhou, China (2014-2023).

Infect Drug Resist. 2025 Jul 12;18:3459-3470. doi: 10.2147/IDR.S530067. eCollection 2025.

Wu L(1)(2), Cai X(3), Xu S(4), Lin X(5), Peng T(1), Jiang X(2)(6).

Author information:
(1)Department of Clinical Laboratory Medicine, The Ding Li Clinical College of

Wenzhou Medical University, Wenzhou Central Hospital, Wenzhou, Zhejiang, 325000, People's Republic of China.
(2)Key Laboratory of Diagnosis and Treatment of New and Recurrent Infectious Diseases of Wenzhou, Wenzhou Sixth People's Hospital, Wenzhou, Zhejiang, 325000, People's Republic of China.
(3)Medical Management Office, Wenzhou Municipal Public Hospital Management Center, Wenzhou, Zhejiang, 325000, People's Republic of China.
(4)Department of Tuberculosis Clinic, The Ding Li Clinical College of Wenzhou Medical University, Wenzhou Central Hospital, Wenzhou, Zhejiang, 325000, People's Republic of China.
(5)Department of Clinical Laboratory Medicine, Yueqing People's Hospital, Wenzhou, Zhejiang, 325600, People's Republic of China.
(6)Department of Infectious Diseases, The Ding Li Clinical College of Wenzhou Medical University, Wenzhou Central Hospital, Wenzhou, Zhejiang, 325000, People's Republic of China.

PURPOSE: This study aimed to elucidate the epidemiological features, drug resistance patterns, and temporal trends among elderly tuberculosis (TB) patients in Wenzhou, China, from 2014 to 2023, providing insights for targeted TB control strategies.
PATIENTS AND METHODS: Data were extracted from 10,993 TB patients registered in the Laboratory Information System of Wenzhou Central Hospital and the Tuberculosis Information Management System of the Chinese Center for Disease Control and Prevention. Patients were divided into elderly (≥60 years, n=2,727) and non-elderly (<60 years, n=8,266) groups. Sociodemographic, clinical, and phenotypic drug susceptibility testing data were analyzed using chi-square tests. Temporal trends in drug resistance were assessed via Joinpoint regression to estimate annual percentage changes (APC).
RESULTS: The elderly group had higher proportions of males (79.65% vs 69.66%), Han ethnicity (99.63% vs 96.35%), and lesions involving ≥3 lung fields (42.35% vs 32.62%), but lower proportions of migrants (20.32% vs 51.20%), urban residents (41.03% vs 53.41%), employed individuals (8.98% vs 32.91%), and pulmonary cavitation (46.75% vs 53.54%). The overall drug-resistant tuberculosis (DR-TB) rate was similar between the elderly and non-elderly groups (20.76% vs 20.30%). However, the elderly group had lower rates of streptomycin (SM) resistance (11.07% vs 12.62%), rifampicin (RFP) resistance (6.20% vs 8.06%), and multidrug-resistant tuberculosis (MDR-TB) (5.39% vs 7.10%). From 2014 to 2023, the overall DR-TB rate among elderly patients decreased from 31.58% to 20.64% (-34.63%), with a significant decline in MDR-TB (APC of -9.9%). Resistance to isoniazid (INH) decreased from 2016 to 2023 (APC -4.0%), and RFP resistance decreased from 2014 to 2021 (APC -10.7%). Significant decreases were also observed among migrant populations (APC -10.1%, 2014-2020), urban residents (APC -8.7%, 2014-2021), and unemployed individuals (APC -4.3%, 2014-2023).
CONCLUSION: Our study revealed that drug resistance among elderly TB patients in

Wenzhou has decreased over the past decade, particularly for MDR-TB and key first-line drugs. However, the elderly group still exhibited distinct epidemiological and drug resistance profiles compared to younger patients. These findings offer clear suggestions for public health policy-making and clinical practice, which can help further reduce the burden of tuberculosis and drug resistance in the elderly population.

DOI: 10.2147/IDR.S530067
PMCID: PMC12266078
PMID: 40671759

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

50. In Vitro and In Silico Evaluation of Isatin-Derived Spirooxindoles as Antituberculosis Drug Candidates.

Chem Biol Drug Des. 2025 Jul;106(1):e70152. doi: 10.1111/cbdd.70152.

de Lima FR(1), de Oliveira Viana J(1)(2), de Castro AC(1), Cristiano R(1)(2), Perelló MA(3), Czeczot AM(3)(4), Bizarro CV(3)(4), Machado P(3)(4)(5), Basso LA(3)(4)(5), Lima-Junior CG(1)(2), Rodrigues-Junior VDS(6), Weber KC(1)(2).

Author information:
(1)Programa de Pós-Graduação em Química, Universidade Federal da Paraíba (UFPB), João Pessoa, Brazil.
(2)National Institute of Science and Technology on Molecular Sciences-INCT-CiMol, João Pessoa, Brazil.
(3)Centro de Pesquisas em Biologia Molecular e Funcional (CPBMF), Instituto Nacional de Ciência e Tecnologia em Tuberculose (INCT-TB), Pontifícia Universidade Católica do Rio Grande do Sul (PUCRS), Porto Alegre, Brazil.
(4)Programa de Pós-Graduação em Biologia Celular e Molecular, Escola de Ciências da Saúde e da Vida, PUCRS, Porto Alegre, Brazil.
(5)Programa de Pós-Graduação em Medicina e Ciências da Saúde, PUCRS, Porto Alegre, Brazil.
(6)Programa de Pós-Graduação em Produtos Naturais e Sintéticos Bioativos, Universidade Federal da Paraíba (UFPB), João Pessoa, Brazil.

Tuberculosis (TB) remains a major global health threat, exacerbated by multidrug-resistant Mycobacterium tuberculosis (MTB) strains. The development of new anti-TB agents is crucial. In this study, 17 isatin derivatives synthesized

by our research group were evaluated for their in vitro activity against MTB strains and the two most potent compounds were assessed for cytotoxicity. Additionally, molecular docking was performed against 22 MTB protein targets to explore possible mechanisms of action, and ADMET predictions were used to determine pharmacokinetic and pharmacodynamic suitability. Also, we investigated the activity of A15, A16, and A17 against two genetically characterized multidrug-resistant clinical isolates (PT-12 and PT-20). As a result, the compounds A16 and A17 exhibited the highest anti-TB activity (MIC = 10 μM for both). Inverse molecular docking indicated the enzyme enoyl-[acyl-carrier-protein] reductase as a potential biological target. Cytotoxicity assays confirmed that A16 and A17 were non-toxic, and ADMET predictions indicated suitable drug-like properties for anti-TB therapy. Notably, A16 and A17 showed inhibitory effects against drug-resistant MTB isolates, with minimum inhibitory concentrations (MICs) ranging from 10 to 20 μM, suggesting their potential to overcome resistance mechanisms linked to mutations in katG and rpoB. These findings highlight A16 and A17 as promising candidates for anti-TB agents, particularly against multidrug-resistant strains.

DOI: 10.1111/cbdd.70152
PMCID: PMC12212626
PMID: 40591553 [Indexed for MEDLINE]

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

51. The prognostic significance of desmoplastic reaction, tumor budding and tumor-infiltrating lymphocytes in esophageal squamous cell carcinomas.

BMC Gastroenterol. 2025 Jul 1;25(1):476. doi: 10.1186/s12876-025-03984-y.

Gunizi OC(1), Altunay B(2), Turgut SD(2), Elpek GO(2).

Author information:
(1)Department of Pathology, Akdeniz University Medical School, Antalya, Turkey. cerengunizi@akdeniz.edu.tr.
(2)Department of Pathology, Akdeniz University Medical School, Antalya, Turkey.

BACKGROUND: Recent research has demonstrated the importance of the tumor microenvironment (TME) in the behavior of solid tumors. Numerous discoveries suggest that tumor progression in a variety of malignancies, including those of the gastrointestinal tract, may be predicted by pathological evaluation of the

desmoplastic reaction (DR), tumor budding (TB) and tumor-infiltrating lymphocytes (TIL). While some studies have demonstrated the prognostic impact of TIL in patients with squamous cell carcinoma of the esophagus (ESCC), the data have not reached agreement. Furthermore, few studies have investigated the relationship of DR and TB with disease progression. The relationships between DR, TB and TIL in these tumors remain to be investigated. Therefore, this study was undertaken to explore the relationships between DR, TB and TIL and histopathological parameters related to tumor behavior and assess their prognostic role in predicting survival in patients with ESCC.
METHODS: The retrospective case series included 98 patients diagnosed with ESCC. DR was assessed on the basis of the maturation of the tumor stroma. TB was evaluated according to the International Tumor Budding Conference (ITBCC) criteria. A semiquantitative method with a 5% threshold value was used to evaluate TIL.
RESULTS: A significant correlation was identified between DR and sex ($p = 0.023$) and between DR and depth of invasion (T) ($p = 0.006$). TB and TIL were correlated with T ($p < 0.001$ and $p = 0.002$), lymph node metastasis (LNM) ($p = 0.006$ and $p = 0.018$), tumor stage ($p < 0.001$) and $p = 0.003$). Although DR was significantly positively correlated with TB ($p < 0.001$), no correlation was detected with TIL. A negative correlation between TIL and TB was also observed ($p = 0.04$). The results of the univariate analysis revealed significant correlations between poor survival rates and T ($p < 0.001$), LNM ($p = 0.002$), stage ($p < 0.001$), DR ($p < 0.001$), TB ($p < 0.001$), and TIL ($p = 0.009$). The multivariate analysis revealed that DR ($p < 0.001$), TB ($p < 0.001$), and T ($p < 0.001$) were independent prognostic factors.
CONCLUSION: Our study emphasized that the assessment of DR and TB can be used to categorize individuals with ESCC for therapy and prognosis. Further research is needed to clarify the prognostic roles of TIL and their subtypes in ESCC and how they are associated with DR, depending on their association with TB.

DOI: 10.1186/s12876-025-03984-y
PMCID: PMC12211902
PMID: 40597640 [Indexed for MEDLINE]

Conflict of interest statement: Declarations. Ethics approval and consent to participate: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. This study was approved by the Ethics Committees of the Akdeniz University School of Medicine (No.13.12.2023/915). Every participant in the study was anonymous, and it was retrospective in nature. Each patient included in the study signed an informed consent form. This article does not contain any studies with human or

animal subjects performed by any of the authors. Consent for publication: Not Applicable. Competing interests: The authors declare no competing interests.

52. Comment on: Risk factors associated with multidrug-resistant tuberculosis in areas with a moderate tuberculosis burden.

Int Health. 2025 Jul 1;17(4):603-604. doi: 10.1093/inthealth/ihae060.

Toledo JPC(1).

Author information:
(1)Department of Theology and Religious Education, De La Salle University, 2401 Taft Avenue, 1004 Manila, Philippines.

DOI: 10.1093/inthealth/ihae060
PMCID: PMC12212191
PMID: 39319562

Conflict of interest statement: The author declares no competing interests.

53. Global burden and trend of tuberculosis in children and adolescents (under 15 years old) from 1990 to 2021, with projections to 2040.

Front Public Health. 2025 Jun 25;13:1578658. doi: 10.3389/fpubh.2025.1578658. eCollection 2025.

Liang Y(1), Wang J(2), Yang J(3), Liu J(4), He X(5).

Author information:
(1)Clinical Experimental Center, Jiangmen Key Laboratory of Clinical Biobanks and Translational Research, Jiangmen Central Hospital, Jiangmen, China.
(2)Queen Mary College, Nanchang University, Nanchang, China.
(3)Department of Public Health and Preventive Medicine, Changzhi Medical College, Changzhi, China.
(4)Department of Biochemistry, Changzhi Medical College, Changzhi, China.
(5)Institute of Evidence-Based Medicine, Heping Hospital Affiliated to Changzhi Medical College, Changzhi, China.

BACKGROUND: Tuberculosis (TB) remains a significant global health issue, but its burden among children and adolescents under 15 years old is not well quantified. This study evaluates TB trends in this age group from 1990 to 2021 and projects future trends through 2040.

METHODS: We used data from the Global Burden of Disease Study (GBD) 2021 to assess the incidence and mortality of TB in children and adolescents (under 15) from 1990 to 2021. A Bayesian age-period-cohort model was employed to project the TB burden.
RESULTS: In 2021, there were 799,047 new TB cases and 81,870 TB-related deaths among children, with an age-standardized incidence rate (ASIR) of 40.01 per 100,000 population and an age-standardized mortality rate (ASMR) of 4.16 per 100,000 population. From 1990 to 2021, the ASIR declined by 2.4% annually, while ASMR decreased by 4.19% per year. However, drug-resistant TB, especially extensively drug-resistant TB, increased significantly. The burden was highest in low-SDI regions, particularly among children under 5, who accounted for over 75% of TB-related deaths. Projections to 2040 indicate continued declines in ASIR and ASMR for all TB forms, including drug-resistant and TB-HIV co-infections.
CONCLUSION: Sustained investment in TB control programs, particularly in low-SDI regions, is crucial. Addressing drug-resistant TB and TB-HIV co-infection should be prioritized in global public health strategies.

DOI: 10.3389/fpubh.2025.1578658
PMCID: PMC12237893
PMID: 40636873 [Indexed for MEDLINE]

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

54. Feasibility and acceptability of GeneXpert MTB/XDR implementation among healthcare workers in three low-middle income African countries.

PLoS One. 2025 Jun 24;20(6):e0326342. doi: 10.1371/journal.pone.0326342. eCollection 2025.

Keller S(1), Naidoo K(2)(3), Zekarias M(4), Israel-Isah S(5), Shaka M(4), Gule G(2)(3), Naidoo A(2)(3), Bathnna M(5), Dlamini-Miti JN(6), Yae K(4), Okpokoro E(5), Abimiku A(5)(7), Bedru A(4), Tiemersma EW(1); TRiAD Study Consortium.

Author information:
(1)KNCV Tuberculosis Foundation, Den Haag, The Netherlands.
(2)Centre for the Aids Programme of Research in South Africa, Durban, KwaZulu-Natal, South Africa.
(3)SAMRC-CAPRISA HIV-TB Pathogenesis and Treatment Research Unit, Doris Duke

Medical Research Institute, University of KwaZulu-Natal, Durban, KwaZulu-Natal, South Africa.
(4)KNCV Tuberculosis Foundation, Ethiopia Office, Addis Ababa, Ethiopia.
(5)International Research Centre of Excellence- Institute of Human Virology, Abuja, Nigeria.
(6)University of the Witwatersrand, Johannesburg, South Africa.
(7)University of Maryland School of Medicine Institute of Human Virology, Baltimore, Maryland, United States of America.

BACKGROUND: Xpert MTB/XDR (Xpert-XDR) testing can significantly shorten time to initiating appropriate drug-resistant tuberculosis (DR-TB) treatment, but its introduction may impact laboratory workflow, especially in laboratories not currently performing drug susceptibility testing. This study evaluated the feasibility and acceptability of implementing the Xpert-XDR for rapid triage and selection of all-oral regimens for DR-TB.
METHOD: This was a multi-country, multi-site qualitative study conducted between July and November 2023, as part of the larger TriAD (Triage test for All oral DR TB drugs) study implemented in South Africa, Ethiopia, and Nigeria. We conducted semi-structured in-depth interviews with clinicians, nurses and laboratory staff at each study site until thematic saturation was achieved. Additionally, we interviewed policy makers (n = 9) and people with TB (PWTB) (n = 11), to provide additional insight on the implementation of this new diagnostic assay.
RESULTS: Healthcare workers (n = 61) found the new workflow feasible and acceptable. It was the increased speed in which PWTB would receive a correct diagnosis and appropriate treatment that provided the biggest benefit to moving to Xpert-XDR for healthcare workers and PWTB. Laboratory staff mentioned that Xpert-XDR had expedited and simplified the laboratory workflows.
Role-appropriate and ongoing training is a key factor in effective implementation as described by policy makers and healthcare workers alike.
Barriers impacting the ability to perform Xpert-XDR included unstable power supply, internet, and temperature control. Additionally, the Xpert MTB/Rif Ultra test has higher sensitivity for the detection of TB than the Xpert-XDR test, leading to discordant test results.
CONCLUSION: This study showed that implementation of Xpert-XDR in health facilities is both feasible and acceptable by all types of healthcare workers. Some barriers with Xpert-XDR are not exclusive to this particular diagnostic tool but are important to address when policy makers are deciding which tools to implement.

DOI: 10.1371/journal.pone.0326342
PMCID: PMC12186877
PMID: 40554504 [Indexed for MEDLINE]

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

55. Effects of missed anti-tuberculosis therapy doses on treatment outcome: a multi-center cohort study.

Lancet Reg Health Am. 2025 Jun 25;48:101162. doi: 10.1016/j.lana.2025.101162. eCollection 2025 Aug.

Ferreira IBB(1)(2), Menezes RC(2)(3)(4), Araújo-Pereira M(2)(3)(4), Rolla VC(5), Kritski AL(6), Cordeiro-Santos M(7)(8), Sterling TR(9), Staats C(9), Amorim G(10), Trajman A(11), Andrade BB(1)(2)(3)(4)(9); RePORT-Brazil Consortium.

Collaborators: Benjamin A, Medeiros Q, Ridolfi F, Gomes-Silva A, Oliveira J, Marine J, Durovni B, Cavalcante S, Rezende A, Bezerra A, Carvalho A, Brito A, Costa A, Spener-Gomes R, Rocha M, Nascimento V, Nogueira B, Andrade A, Silva E.

Author information:
(1)Escola Bahiana de Medicina e Saúde Pública, Pós-graduação em Medicina e Saúde Humana, Salvador, Brazil.
(2)Multinational Organization Network Sponsoring Translational and Epidemiological Research (MONSTER) Institute, Salvador, Brazil.
(3)Laboratório de Pesquisa Clínica e Translacional, Instituto Gonçalo Muniz, Fundação Oswaldo Cruz, Salvador, Brazil.
(4)Curso de Medicina, Faculdade ZARNS, Clariens Educação, Salvador, Brazil.
(5)Laboratório de Pesquisa Clínica em Micobacterioses, Instituto Nacional de Infectologia Evandro Chagas/FIOCRUZ, Rio de Janeiro, Brazil.
(6)Universidade Federal do Rio de Janeiro, Programa Acadêmico de Tuberculose, Rio de Janeiro, Brazil.
(7)Grupo de Pesquisa em Tuberculose, Fundação Medicina Tropical Doutor Heitor Vieira Dourado, Manaus, Brazil.
(8)Curso de Medicina, Universidade do Estado do Amazonas (UEA), Manaus, Brazil.
(9)Division of Infectious Diseases, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, USA.
(10)Department of Biostatistics, Vanderbilt University Medical Center, Nashville, USA.
(11)Departamento de Clínica Médica, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil.

BACKGROUND: Tuberculosis (TB) remains a leading cause of infectious disease mortality globally. Although directly observed therapy (DOT) has been widely implemented to improve adherence, nonadherence continues to compromise treatment success rates, especially in real-world settings. Therefore, this study aims to assess the impact of missed doses on TB treatment outcomes.
METHODS: Prospective study that followed adults with drug-sensitive TB for two years after TB treatment initiation at five clinical centers of the RePORT-Brazil cohort between June 2015 and June 2019. Participants not in DOT or followed for less than 30 days were excluded. Nonadherence was defined as the percentage of missed doses relative to the prescribed regimen, monitored daily through DOT. The primary composite outcome comprised treatment failure, disease recurrence, drug resistance, death, or loss to follow-up (LTFU) after 30 days of treatment. Associations were assessed with multivariable logistic regression.
FINDINGS: Among the 578 participants analyzed, 218 (37·7%) experienced unfavorable outcomes. Overall, 23% of participants missed more than 10% of prescribed doses, and this group had an 81·2% likelihood of experiencing unfavorable outcomes, compared to only 21·6% among those with complete adherence. A significant association was observed between the percentage of missed doses and unfavorable outcomes (adjusted OR: 1·11, 95% CI: 1·07-1·14, p-value < 0·0001).
INTERPRETATION: Even minor nonadherence in TB treatment was associated with an increased risk of unfavorable outcomes, highlighting the role of adherence in successful TB care.
FUNDING: Fundação Oswaldo Cruz, Fundação José Silveira, Departamento de Ciência e Tecnologia, US National Institute of Allergy and Infectious Diseases.

DOI: 10.1016/j.lana.2025.101162
PMCID: PMC12246921
PMID: 40657430

Conflict of interest statement: We declare no competing interests.

56.Diverse impacts of different rpoB mutations on the anti-tuberculosis efficacy of Capreomycin.

EBioMedicine. 2025 Jul;117:105776. doi: 10.1016/j.ebiom.2025.105776. Epub 2025 May 30.

Xu JT(1), Li K(2), Lin Y(1), Cheng T(1), Gu J(3), Chen YK(4), Yu JF(5), Deng JY(6).

Author information:
(1)Wuhan Institute of Virology, Chinese Academy of Sciences, Wuhan 430071, China; University of Chinese Academy of Sciences, Beijing 100049, China.
(2)Department of Infectious Diseases, Chongqing Public Health Medical Center, Chongqing 400036, China.
(3)Wuhan Institute of Virology, Chinese Academy of Sciences, Wuhan 430071, China.
(4)Department of Infectious Diseases, Chongqing Public Health Medical Center, Chongqing 400036, China. Electronic address: yaokaichen@hotmail.com.
(5)Wuhan Institute of Virology, Chinese Academy of Sciences, Wuhan 430071, China. Electronic address: yujifang@wh.iov.cn.
(6)Wuhan Institute of Virology, Chinese Academy of Sciences, Wuhan 430071, China. Electronic address: dengjy@wh.iov.cn.

BACKGROUND: Since the discovery of streptomycin in the 1940s, more than a dozen drugs have been continuously introduced into tuberculosis (TB) therapy. However, limited attention has been paid to the collateral effects of drug resistance evolution in Mycobacterium tuberculosis (Mtb). Recently, we observed a clear discordance between the capreomycin (CAP) susceptibility of rifampicin-resistant (RR) Mtb clinical isolates and the adverse outcomes associated with CAP treatment, indicating potential collateral effects between rpoB mutations and CAP. To explore this relationship, we integrated clinical isolate data, experimental evolution data, phenotypic data, sequencing data, and genome-wide association studies (GWAS).
METHODS: We analysed the correlations between CAP resistance and rpoB mutations at various loci based on phenotypic drug susceptibility testing (pDST) profiles and rpoB sequencing data from 565 RR Mtb isolates collected in southwestern China. To validate the clinical observations, we screened RR mutants of Mtb H37Rv and conducted rpoB sequencing to characterise the mutation sites. Additionally, we constructed various rpoB mutants in Mycobacterium smegmatis (Ms). We then examined the impact of these mutations on the efficacy of CAP through minimum inhibitory concentration (MIC) tests and time-kill assays in both Mtb and Ms rpoB mutants. Furthermore, we investigated the influence of three major rpoB mutations on the frequency of occurrence of rrs A1401G-associated with CAP resistance-using a GWAS of 607 Mtb genomes from a global dataset.
FINDINGS: By analysing 565 clinical isolates from southwestern China, we found that the CAP resistance in isolates with a single mutation at rpoB site 445 was significantly lower than in those with a single mutation at other sites ($P < 0.05$, Pearson chi-square test and Fisher exact test; odds ratio = 0.272). In contrast, the opposite trend was observed in isolates with a single mutation at rpoB site 435 ($P < 0.001$, Pearson chi-square test and Fisher exact test; odds ratio = 3.067). Subsequently, using laboratory-evolved RR mutants, we demonstrated that mutations at rpoB site 445 or site 441 enhanced the

bactericidal effect of CAP. However, the opposite result was observed in mutants with mutations at rpoB site 435. Furthermore, we found that the occurrence frequency of the rrs A1401G mutation was significantly lower in clinical isolates with rpoB mutations at site 445, but significantly higher in those with mutations at site 435.
INTERPRETATION: Although rpoB mutations in Mtb did not affect the MIC of CAP, they influenced its bactericidal effect, highlighting the need for time-kill assays when investigating collateral effects. Different rpoB mutations may exert diverse impacts on the bactericidal effect of CAP-or CAP tolerance-underscoring the complexity of collateral effects and supporting the use of targeted sequencing in the molecular diagnosis of RR Mtb. As RNA polymerase plays a central role in bacterial RNA transcription, it regulates most metabolic processes in Mtb. Thus, different rpoB mutations may elicit distinct gene expression profiles upon CAP treatment, a hypothesis warranting further investigation. Additional clinical studies are needed to verify whether the adverse outcomes of CAP treatment are associated with infections caused by strains harbouring rpoB mutations at site 435. If so, such outcomes could be mitigated through rational drug regimens guided by precise molecular diagnosis. This study provides insights into the collateral effects of drug resistance mutations and advances the case for precision medicine in treating infections caused by drug-resistant bacteria.
FUNDING: Funding for this study was provided by the National Key Research and Development Program of China (Grant no. 2021YFA1300901).

DOI: 10.1016/j.ebiom.2025.105776
PMCID: PMC12166843
PMID: 40449326 [Indexed for MEDLINE]

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

57.High proportion of tuberculosis recent transmission in rural areas of Northeastern China: a 3-year prospective population-based genotypic and spatial analysis in Hinggan League, China.

Microbiol Spectr. 2025 Jul 11:e0016925. doi: 10.1128/spectrum.00169-25. Online ahead of print.

Ou X(#)(1), Li X(#)(2), Pei S(#)(3), Zhao B(1), Feng L(4), Teng C(1), Lu Y(2), Zhu H(1), Zhou Y(1), Xia H(1), Liu Z(5), Wang X(5), Wang Y(6), Anthony R(7), Zhao Y(1).

Author information:
(1)National Key Laboratory of Intelligent Tracking and Forecasting for Infectious Diseases, National Center for Tuberculosis Control and Prevention, Chinese Center for Disease Control and Prevention, Beijing, China.
(2)Key Laboratory of Precision Medicine in Diagnosis and Monitoring Research of Zhejiang Province, Hangzhou, Zhejiang, China.
(3)School of Public Health, Peking University, Beijing, China.
(4)Department of Microbiology, Hinggan League Center for Disease Control and Prevention, Ulanhot, China.
(5)Department of Tuberculosis Control and Prevention, Zhejiang Provincial Center for Disease Control and Prevention, Hangzhou, China.
(6)Administration Office, Medical Insurance Service Center of Ulanhot City, Ulanhot, China.
(7)Centre for Infectious Disease Control, National Institute for Public Health and the Environment, Bilthoven, the Netherlands.
(#)Contributed equally

Tuberculosis (TB) remains a significant public health challenge in China, particularly in rural areas like Hinggan League (HL), Inner Mongolia. Understanding the genetic diversity and transmission dynamics of Mycobacterium tuberculosis (MTB) strains is crucial for effective TB control. We conducted a prospective study from 2021 to 2023, sequencing 221 MTB isolates from HL. After quality control, 210 cases were analyzed. The genomic clustering rate was calculated to evaluate the level of recent transmission. Risk factors were identified by logistic regression analysis. Geospatial analysis was conducted with kernel density estimation. The majority of strains belonged to sub-lineage 2.2.1 in lineage 2 (L2), also known as the Beijing family (89.0%, 187/210), while the remainder belonged to lineage 4 (L4). L2 strains showed greater genetic similarity and shorter branch lengths compared with L4 strains. The overall drug resistance rate was 21.9%, with six multidrug-resistant TB (MDR-TB) and five pre-extensively drug resistant TB (pre-XDR-TB) cases identified. Almost half of the strains belonged to putative transmission clusters within 10 SNPs. Logistic regression analysis identified living in Jalaid Banner and being infected by L2 strains as significant risk factors for recent transmission. Spatial analysis identified spatial aggregation of TB cases in the eastern region of HL, with a hotspot for recent transmission in Jalaid Banner. The temporal distribution of TB cases in HL exhibited seasonal fluctuations, with diagnosis rates peaking in the first half of each year, and a notable increase in clustered cases in 2022. This study provides insights into the molecular epidemiology and transmission dynamics of TB in HL. Our results underscore the ongoing problem of TB transmission in rural settings, indicating the need for targeted interventions. These findings are vital for informing TB control strategies in HL and similar settings.IMPORTANCETuberculosis (TB) remains a

major public health problem in China. This study provides insights into the molecular epidemiology and transmission dynamics of TB in rural areas (Hinggan League [HL], Inner Mongolia) in China. Nearly half of the enrolled TB cases were attributed to recent transmission, a proportion higher than that observed in other rural areas in China (31.4%), highlighting the significance of recent transmission in driving the TB epidemic in this region. Only 19.6% of all drug-resistant TB (DR-TB) cases were found within putative transmission clusters, indicating a lower proportion compared with the previous studies, which indicated that DR-TB is more associated with the de novo evolution of resistance within patients. Spatial analysis showed that the TB epidemic was concentrated in densely populated areas in eastern HL. The findings identified epidemiological differences within HL, highlighting the importance of targeted interventions and surveillance to control the spread of TB in HL.

DOI: 10.1128/spectrum.00169-25
PMID: 40643231

58. Safety and Tolerability of Contezolid Versus Linezolid for Short-Term Treatment of Rifampicin-Resistant Pulmonary Tuberculosis: A Randomized Controlled Study.

Infect Drug Resist. 2025 Jul 4;18:3307-3315. doi: 10.2147/IDR.S516991. eCollection 2025.

Wang J(#)(1), Xue Y(#)(1), Nie W(1), Ma L(1), Chu N(1), Du Y(1).

Author information:
(1)Tuberculosis Department, Beijing Chest Hospital, Capital Medical University, Beijing Tuberculosis and Thoracic Tumor Research Institute, Beijing, People's Republic of China.
(#)Contributed equally

PURPOSE: Linezolid is a core drug used to treat rifampicin-resistant tuberculosis (RR-TB) and multidrug-resistant tuberculosis (MDR-TB). However, adverse events (AEs) have limited its clinical application. Safer alternatives to linezolid are needed to address the safety concerns.
PATIENTS AND METHODS: A total of 27 patients with RR-TB (including MDR-TB) were randomly assigned to receive either contezolid (n=14) or linezolid (n=13) in combination with standardized background anti-TB regimens, that is, linezolid-bedaquiline (pyrazinamide)-levofloxacin (moxifloxacin)-cycloserine-clofazimine or contezolid-bedaquiline (pyrazinamide)-levofloxacin (moxifloxacin)-cycloserine-clofazimine. The dosage was 600 mg q12h for linezolid, and 800 mg q12h for contezolid. AE data were collected during the 2-month treatment period to analyze the characteristics,

severity, onset time, duration, drug relatedness, management, and outcome of the adverse drug reactions.
RESULTS: The median (range) age of contezolid- and linezolid-treated patients was 40.9 (26-65) and 36.7 (18-65) years, respectively. The incidence of AEs was 14.3% (2/14) in contezolid-treated patients and 92.3% (12/13) in linezolid group. All drug-related AEs in contezolid group were gastrointestinal reactions (nausea and vomiting one case each). No peripheral neuropathy or myelosuppression AEs were observed. The AEs in linezolid group included anemia (30.8%, 4/13), peripheral neuropathy (53.8%, 7/13), and gastrointestinal reactions (23.1%, 3/13). Dose reduction or discontinuation was required for linezolid in 84.6% (11/13) of patients. The anti-TB efficacy of contezolid and linezolid was comparable in terms of sputum culture conversion rate and imaging-confirmed lesion absorption rate after treatment for 2 months.
CONCLUSION: Contezolid may be a safer alternative to linezolid based on AE incidence in the treatment of multidrug-resistant tuberculosis for two months.
CLINICAL TRIAL REGISTRATION: This study was registered at https://www.chictr.org.cn (identifier: ChiCTR2300074234).

DOI: 10.2147/IDR.S516991
PMCID: PMC12238134
PMID: 40635770

Conflict of interest statement: The authors declared no potential conflict of interest with respect to the research, authorship, and/or publication of this article.

59. Comparative Analysis of 2 Diagnostic Devices for Detection of Mycobacterium tuberculosis and Drug Resistance in Almaty, Kazakhstan, to Determine the Optimal Diagnostic for Local Needs.

Open Forum Infect Dis. 2025 Jun 13;12(7):ofaf342. doi: 10.1093/ofid/ofaf342. eCollection 2025 Jul.

Bartels JGE(1), Takenov N(2), Chingissova L(2), Rakisheva A(3), Eleusizova A(3), Bismilda V(2), Yeraliyeva L(2), Ben Amor Y(1).

Author information:
(1)Center for Sustainable Development, Columbia University, New York, New York, USA.
(2)National Tuberculosis Reference Laboratory, National Scientific Center of Phthisiopulmonology, Almaty, Kazakhstan.

(3)Center of Phthisiopulmonology Almaty, Almaty, Kazakhstan.

BACKGROUND: Rapid, accurate detection of Mycobacterium tuberculosis and drug resistance is crucial to reduce tuberculosis (TB) burden and prevent development of drug resistance in high-burden drug-resistant TB regions.
METHODS: From December 2021 to July 2022, sputum samples from 1214 adult patients with presumptive TB in Almaty, Kazakhstan, were tested by BD MAX MDR-TB (Becton Dickinson), Cepheid Xpert MTB/RIF, and mycobacterial growth indicator tube (MGIT) liquid culture for detection of TB and drug resistance to rifampicin (RIF) and isoniazid (INH).
RESULTS: When compared with MGIT, BD MAX sensitivity and specificity for TB detection were 90% and 87%, and Xpert MTB/RIF results were 86% and 92%. For RIF resistance, BD MAX sensitivity and specificity were 91% and 95%, and Xpert MTB/RIF results were 94% and 92%. For INH resistance, BD MAX sensitivity and specificity were 98% and 97%. Whole genome sequencing was conducted for 24 samples with discordant RIF resistance results among the 3 devices to determine mutations related to resistance. When compared with a composite standard based on whole genome sequencing and MGIT, Xpert MTB/RIF had higher sensitivity and specificity for RIF resistance than BD MAX.
CONCLUSIONS: Countries with high burden of drug-resistant TB should carry out national prevalence surveys to assess rates of multidrug-resistant TB and INH monoresistance. Those with higher rates should consider adopting BD MAX due to its ability to accurately diagnose RIF and INH resistance.

DOI: 10.1093/ofid/ofaf342
PMCID: PMC12232910
PMID: 40626055

Conflict of interest statement: Potential conflicts of interest. All authors: No reported conflicts.

60. Longitudinal phenotypic and genomic evidence revealing increased risk of drug resistance accumulation in tuberculosis patients in the counties of central China.

Microbiol Spectr. 2025 Jun 23:e0038025. doi: 10.1128/spectrum.00380-25. Online ahead of print.

Wang F-L(#)(1), Chen R(#)(2), Xu Q(#)(3), Wang X-Q(3), Tao F-X(4), Huang Z-K(1), Zhang Y-T(1), Chen S-Q(3), Wu X-J(3), Cao H-Y(3), Jiang Q(1).

Author information:
(1)Department of Epidemiology and Biostatistics, School of Public Health, Research Center of Public Health, Renmin Hospital of Wuhan University, Wuhan University, Wuhan, Hubei, China.
(2)Department of Vaccine, Wuchang District Center for Disease Control and Prevention, Wuhan, Hubei, China.
(3)Department of Public Health, Laboratory of Clinical Microbiology, The Second People's Hospital of Xianning City (Xianning Hospital of Tuberculosis Treatment and Control), Xianning, Hubei, China.
(4)Department of Public Health, The Fourth Hospital of Wuhan, Wuhan, Hubei, China.
(#)Contributed equally

Drug-resistant tuberculosis (DR-TB) disproportionately affects rural China, yet the molecular and epidemiological drivers of this disparity remain inadequately explored. This study investigates resistance evolution and transmission dynamics in Xianning, China, using longitudinal data from 3,865 culture-positive pulmonary tuberculosis patients (2016-2023). Phenotypic drug susceptibility testing for 14 commonly used anti-tuberculosis drugs showed a stable multidrug-resistant tuberculosis (MDR-TB) rate of 6.6%, while mono-resistance increased from 8.5% to 12.9% over the study period. Notably, 19.3% (53/275) of patients with ≥2 months of culture positivity developed new phenotypic resistance during treatment. Whole-genome sequencing of strains from the last two years identified resistance accumulation through two additional mechanisms: (i) acquisition of resistance via unfixed mutations in individuals and (ii) transmitted strains harboring novel resistance-conferring mutations absent in parental clones within genomic clusters. For the combined cases of resistance accumulation, multivariable logistic regression revealed that baseline drug resistance increased the risk more than threefold (aOR = 3.65-5.28, varying by resistance type), while rural residence independently doubled the risk (aOR = 2.60, 95% confidence interval:1.11-6.49). Furthermore, three of five genomic clusters with resistance accumulation exhibited urban-rural transmission, highlighting risks linked to cross-district care-seeking. These findings underscore how systemic healthcare barriers in rural China drive DR-TB through both treatment failures and strain transmission. Urgent action is needed to decentralize rapid resistance screening and implement tiered care models in primary clinics to curb transmission and mitigate the expanding DR-TB threat.IMPORTANCEThe ongoing epidemic of drug-resistant tuberculosis (DR-TB) in resource-poor settings poses a major public health challenge. This study sheds light on the evolution of DR-TB and its community transmission dynamics in central rural China, suggesting that unequal healthcare may exacerbate resistance accumulation risks by driving acquired resistance through inadequate treatment as well as facilitating strain transmission with escalating drug

resistance. These findings emphasize the critical need for decentralized, rapid drug-resistance screening, and enhanced diagnosis and treatment strategies in primary care settings, prioritizing vulnerable populations to curb this growing threat.

DOI: 10.1128/spectrum.00380-25
PMID: 40548705

61.Targeted next-generation sequencing: a promising approach for Mycobacterium tuberculosis detection and drug resistance when applied in paucibacillary clinical samples.

Microbiol Spectr. 2025 Jul;13(7):e0312724. doi: 10.1128/spectrum.03127-24. Epub 2025 Jun 10.

Jin W(#)(1), Wang M(#)(2), Wang Y(#)(3), Zhu B(1), Wang Q(1), Zhou C(4), Li P(5), Hu C(3), Liu J(3), Pan J(1), Chen J(#)(3), Hu B(#)(1).

Author information:
(1)Department of Infectious Diseases, Zhongshan Hospital, Fudan University, Shanghai, China.
(2)Department of Infection Management, Zhongshan Hospital (Xiamen), Fudan University, Xiamen, Fujian, China.
(3)Guangzhou KingCreate Biotechnology Co., Ltd., Guangzhou, Guangdong, China.
(4)Department of Microbiology, Zhongshan Hospital, Fudan University, Shanghai, China.
(5)KingMed Diagnostics, Guangzhou, Guangdong, China.
(#)Contributed equally

Tuberculosis (TB) returns to be the leading infectious killer globally after coronavirus disease 2019. The World Health Organization (WHO) formally included targeted next-generation sequencing (tNGS) in its list of recommendations for Mycobacterium tuberculosis (MTB) and drug resistance (DR). In this study, we explored the application of various clinical sample types for TB diagnosis and DR profiles. In comparison to the composite reference standard, the overall sensitivity values of culture, Xpert, metagenomic next-generation sequencing (mNGS), and tNGS were 0.458, 0.614, 0.772, and 0.760, respectively. tNGS had sensitivity similar to mNGS, which had advantages over culture and Xpert, respectively, despite different classification of sample types. In comparison to the microbiological reference standard, the overall sensitivity values of culture, Xpert, mNGS, and tNGS were 0.606, 0.811, 0.856, and 0.884, respectively. Suprisingly, in extrapulmonary tissue and serous effusion, mNGS and tNGS had advantages over Xpert. DR-related mutations were detected in 15

cases (13.2%). There were 51 (44.7%) applicable for all DR genes, with 22 (19.3%) not applicable for DR genes. DR genes were partially applicable in 41 (36.0%) samples. However, in culture-negative TB cases, tNGS can additionally provide 52.7% first-line DR profiles. Sanger sequencing was performed on 14 samples to confirm gene mutation identified by tNGS, and the results were entirely consistent. It was concluded that the tNGS assay was a promising approach in the initial diagnostic test of MTB and DR-related genes in different clinical samples, even for the smear- and culture-negative paucibacillary samples.IMPORTANCEtNGS combines gene-specific amplification with next-generation sequencing to detect MTB and drug-resistant genes by amplifying numerous loci directly from clinical samples. The WHO implemented tNGS for the purpose of monitoring respiratory specimens for MTB detection and DR-TB due to its high sensitivity and specificity, culture independence, and ability to report heterogeneous/silent mutations. The sensitivity outperformed both culture and Xpert, and the turnaround time was significantly less than that of culture-based assays. The tNGS assay used in this study costs USD 96 and has a 12 hour turnaround time. Nonetheless, tNGS has a great deal of promise for enhancing TB detection while also addressing DR strains.

DOI: 10.1128/spectrum.03127-24
PMCID: PMC12211088
PMID: 40492765 [Indexed for MEDLINE]

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

62. Rapid detection of rifampin resistance in Mycobacterium tuberculosis using nucleotide MALDI-TOF MS: a comparative study with phenotypic drug susceptibility testing and DNA sequencing.

Microbiol Spectr. 2025 Jul;13(7):e0048325. doi: 10.1128/spectrum.00483-25. Epub 2025 May 30.

Zhang J(#)(1), Zhang H(#)(2), Wang J(#)(1), Sun W(1), Liang Y(1), Yang Y(1), Ma Q(2), Wu X(1).

Author information:
(1)Beijing Key Laboratory of New Techniques of Tuberculosis Diagnosis and Treatment, Institute of Tuberculosis Research, Senior Department of Tuberculosis, The Eighth Medical Center of PLA General Hospital, Beijing, China.
(2)Bioyong Technologies Inc., Beijing, China.
(#)Contributed equally

Rifampin (RIF) resistance in Mycobacterium tuberculosis (M.tb) is primarily caused by mutations in the rpoB gene. Rapid and accurate detection of RIF resistance is critical for effective tuberculosis (TB) control. Nucleotide matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) is an emerging technology used to detect RIF resistance-associated rpoB mutations in 210 M.tb clinical isolates, including 107 RIF-sensitive and 103 RIF-resistant strains, as determined by phenotypic drug susceptibility testing (DST). DNA sequencing was used as the reference method to validate nucleotide MALDI-TOF MS results. Nucleotide MALDI-TOF MS demonstrated a sensitivity of 93.2%, specificity of 98.1%, and an overall accuracy of 95.7% compared to phenotypic DST. The Kappa value between nucleotide MALDI-TOF MS and phenotypic DST was 0.91, indicating excellent agreement. DNA sequencing confirmed that nucleotide MALDI-TOF MS successfully identified RIF resistance-associated mutations, particularly in codons 450, 445, and 435 of the rpoB gene. Among the 61 isolates analyzed by DNA sequencing, nucleotide MALDI-TOF MS and sequencing results were consistent for 52 of 56 RIF-resistant strains and all five RIF-sensitive strains, with an overall concordance of 93.4%. Importantly, nucleotide MALDI-TOF MS accurately detected heteroresistance in eight isolates (14.3%), confirmed by sequencing. These results support that nucleotide MALDI-TOF MS is a rapid, accurate, and reliable method for detecting rpoB mutations associated with RIF resistance in M.tb. Its high concordance with DNA sequencing, excellent diagnostic performance, and ability to identify heteroresistance highlight its potential as a valuable tool for early TB diagnostics and improve the precision of chemotherapy regimen development.IMPORTANCEThe emergence of multidrug-resistant tuberculosis (MDR-TB) and rifampin-resistant tuberculosis (RR-TB) poses a significant challenge to global tuberculosis (TB) control efforts. Rifampin (RIF) resistance is a critical marker for MDR-TB, which requires more complex, prolonged, and costly treatment regimens. Early and accurate detection of RIF resistance is crucial for effective TB control. This study evaluates the performance of nucleotide MALDI-TOF MS, an innovative technology, for detecting RIF resistance-associated mutations in the rpoB gene. The method demonstrates high sensitivity (93.2%) and specificity (98.1%), with the added advantage of identifying heteroresistance, capabilities that are lacking in conventional methods. These capabilities are crucial for early diagnosis, guiding personalized treatment regimens, and curbing the transmission of drug-resistant TB. The findings demonstrate that nucleotide MALDI-TOF MS provides a rapid, high-throughput, and cost-effective alternative for detecting rpoB gene mutations associated with RIF resistance.

DOI: 10.1128/spectrum.00483-25
PMCID: PMC12210853
PMID: 40445194 [Indexed for MEDLINE]

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

63. Linking genetic and phenotypic bedaquiline resistance in Mycobacterium tuberculosis strains from Georgia.

PLoS One. 2025 Jul 15;20(7):e0326794. doi: 10.1371/journal.pone.0326794. eCollection 2025.

Maghradze N(1)(2)(3), Loiseau C(1)(2), Goig GA(1)(2), Bablishvili N(3), Jugheli L(1)(2), Borrell S(1)(2), Tukvadze N(1)(2)(3), Kempker RR(4)(5), Avaliani Z(3), Gagneux S(1)(2).

Author information:
(1)Swiss Tropical and Public Health Institute, Basel, Switzerland.
(2)University of Basel, Basel, Switzerland.
(3)National Center for Tuberculosis and Lung Diseases (NCTLD), Tbilisi, Georgia.
(4)Division of Infectious Diseases, Department of Medicine, Emory University School of Medicine, Atlanta, Georgia, United States of America.
(5)Departments of Epidemiology and Global Health, Rollins School of Public Health of Emory University, Atlanta, Georgia, United States of America.

INTRODUCTION: Resistance to bedaquiline - a novel, promising medication against tuberculosis (TB), is already emerging, and uncertainties regarding the role of the different resistance-conferring mutations complicate the development of molecular diagnostic tools for detecting resistance. Mutations in the three genes atpE, pepQ, and Rv0678 have been associated with increased minimum inhibitory concentrations (MICs) to bedaquiline in Mycobacterium tuberculosis (Mtb). Here, we studied the effect of known and novel mutations in these genes on the phenotypic susceptibility to bedaquiline in Mtb isolates from patients with drug-resistant TB in the country of Georgia.
METHODS: We used retrospective Mtb isolates (2011-2019) with whole-genome sequencing data, and prospectively collected diagnostic isolates with phenotypic resistance (2019-2022) to bedaquiline at the Georgian National Reference Laboratory. We determined bedaquiline MIC values using the SensititreTM MYCOTB MIC plate. MIC of 0.12 μg/mL was defined as borderline and MIC ≥ 0.25 μg/mL as a resistant isolate. A phylogeny was inferred to assess the likely role of the identified variants in bedaquiline resistance, while taking into consideration population structure of the strains analyzed.
RESULTS: We analyzed a total of 69 Mtb isolates and identified 61 mutations across the three target genes. Seventeen (27.8%) of these variants were associated with borderline (0.12 μg/mL) or resistant (≥0.25 μg/mL) MICs to bedaquiline. In addition to six previously described bedaquiline resistance-conferring mutations in atpE and Rv0678, we identified two novel variants in Rv0678 (Leu95Ser and Ile108fs) likely involved in bedaquiline

resistance. We found a Tyr92Cys mutation in Rv0678 in two epidemiologically linked isolates, which likely emerged as a consequence of previous exposure to clofazimine.
CONCLUSION: Consistent with previous reports, our study confirms that mutations in Rv0678 are the most frequent cause of bedaquiline resistance in Georgia, in addition to an increasing clinical relevance of mutations in atpE, while the role of pepQ mutations remains to be defined.

DOI: 10.1371/journal.pone.0326794
PMCID: PMC12262877
PMID: 40663566 [Indexed for MEDLINE]

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

64. Synthesis, Antimycobacterial Activity, and Computational Insight of Novel 1,4-Benzoxazin-2-one Derivatives as Promising Candidates against Multidrug-Resistant Mycobacterium Tuberculosis.

ChemMedChem. 2025 Jul 18;20(14):e202500073. doi: 10.1002/cmdc.202500073. Epub 2025 Jun 10.

Mamolo MG(1), Carosati E(1), Pasin D(2), De Logu A(3), Cabiddu G(3), Jukič M(4)(5), Zampieri D(1).

Author information:
(1)Department of Chemistry and Pharmaceutical Sciences, University of Trieste, Via L. Giorgieri 1, 34127, Trieste, Italy.
(2)S.O.C. Experimental and Clinical Pharmacology, IRCSS, RO Aviano, Via F. Gallini 2, 33081, Aviano, Italy.
(3)Department of Life and Environmental Sciences, University of Cagliari, Cittadella Universitaria di Monserrato, Monserrato, 09042, Cagliari, Italy.
(4)Faculty of Chemistry and Chemical Engineering, University of Maribor, Smetanova ulica 17, SI-2000, Maribor, Slovenia.
(5)Faculty of Mathematics, Natural Sciences and Information Technologies, University of Primorska, Glagoljaška ulica 8, SI-6000, Koper, Slovenia.

In the search for new antitubercular agents, a series of 1,4-benzoxazinone-based

compounds is designed, synthesized, and evaluated. These molecules show potent antimycobacterial activity, with a minimum inhibitory concentration between 2 and 8 μg mL-1. This interesting profile includes activity against several drug-resistant strains and minimal cytotoxicity against mammalian Vero cells. Structural similarities with analogs from the literature are reinforced by molecular docking and molecular dynamics simulations, suggesting that inhibition of the menaquinone-B enzyme as a potential mechanism of action. In addition, the active compounds exhibit favorable predicted Absorption, Distribuition, Metabolism, and Excretion (ADME) properties, indicating their potential for oral administration in humans.

DOI: 10.1002/cmdc.202500073
PMCID: PMC12276033
PMID: 40365658 [Indexed for MEDLINE]

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

65. Discovery of novel fluorescent amino-pyrazolines that detect and kill Mycobacterium tuberculosis.

Eur J Med Chem. 2025 Jun 24;297:117889. doi: 10.1016/j.ejmech.2025.117889.

Cui Y(1), Lanne A(2), Avula S(3), Hama Salih MA(4), Peng X(5), Milne G(6), Jones G(6), Ritchie J(6), Zhao Y(7), Frampton J(8), Tortorella M(3), Fossey JS(1), Alderwick LJ(9), Neagoie C(10).

Author information:
(1)School of Chemistry, University of Birmingham, Edgbaston, Birmingham, West Midlands, B15 2TT, UK.
(2)Institute of Microbiology and Infection, School of Biosciences, University of Birmingham, Edgbaston, Birmingham, West Midlands, B15 2TT, UK.
(3)Centre for Regenerative, Medicine and Health, Hong Kong Institute of Science Innovation, Chinese Academy of Sciences, 5/F, 15W Science Park West Avenue, the Hong Kong Special Administrative Region of China.
(4)School of Chemistry, University of Birmingham, Edgbaston, Birmingham, West Midlands, B15 2TT, UK; College of Health and Medical Technology, Sulaimani Polytechnic University, Sulaimani, Iraq.
(5)Guangzhou National Laboratory, Guangzhou International Bio Island, Guangzhou 510005, China.
(6)Sygnature Discovery, The Discovery Building, BioCity, Pennyfoot Street,

Nottingham, NG1 1GR, UK.
(7)School of Chemistry, University of Birmingham, Edgbaston, Birmingham, West Midlands, B15 2TT, UK; X-Ray Crystallography Facility, School of Chemistry, University of Birmingham, Edgbaston, Birmingham, West Midlands, B15 2TT, UK.
(8)College of Medical and Dental Sciences, University of Birmingham, Edgbaston, Birmingham, West Midlands, B15 2TT, UK.
(9)Institute of Microbiology and Infection, School of Biosciences, University of Birmingham, Edgbaston, Birmingham, West Midlands, B15 2TT, UK; Discovery Sciences, Charles River Laboratories, Chesterford Research Park, CB10 1XL, UK. Electronic address: luke.alderwick@crl.com.
(10)Centre for Regenerative, Medicine and Health, Hong Kong Institute of Science Innovation, Chinese Academy of Sciences, 5/F, 15W Science Park West Avenue, the Hong Kong Special Administrative Region of China. Electronic address: cleopatra.neagoie@crmh-cas.org.hk.

The emergence of multidrug-resistant Mycobacterium tuberculosis (MDR-TB) necessitates novel therapeutics with distinct mechanisms. Here, we report amino-pyrazoline derivatives as a new class of dual-functional antimycobacterial agents, integrating potent bactericidal activity with fluorescence-based bacterial imaging. Initial screening identified AP-07 as a promising hit compound (MIC99: 40 μM against Mycobacterium smegmatis, 49 μM against Mycobacterium bovis BCG). Structure-based optimization led to the discovery of AP-02 and AP-05 as lead compounds, with enhanced activity (MIC99: 13-16 μM against M. smegmatis; 20-25 μM against M. bovis BCG). Additionally, spontaneous resistance assays detected no resistant colonies, suggesting a low risk of resistance development. Mechanistic studies confirmed Ag85C as the primary molecular target, disrupting late-stage mycolic acid biosynthesis and impairing cell wall integrity. Notably, pyrazoline derivatives exhibit intrinsic fluorescence, selectively labeling intracellular mycobacteria while remaining non-toxic to host macrophages, enabling real-time bacterial imaging. This work establishes fluorescent amino-pyrazolines as a promising foundation for next-generation antitubercular agents, bridging diagnostics and therapy in tuberculosis drug discovery.

DOI: 10.1016/j.ejmech.2025.117889
PMID: 40592183

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.

66. Endemic transmission of a Mycobacterium tuberculosis L2.2.M3 sublineage of the L2 lineage within Colon, Panama: A prospective study.

Infect Genet Evol. 2025 Jul;131:105749. doi: 10.1016/j.meegid.2025.105749. Epub 2025 Apr 22.

Acosta F(1), Candanedo D(2), Patel P(1), Llanes A(1), Ku JE(1), Salazar K(2), Morán M(1), Sambrano D(1), Jurado J(3), Martínez I(4), Garibaldi L(3), Delgado M(3), Solís L(4), Luque O(4), Da Silva K(5), Andrews J(5), Goodridge A(6).

Author information:
(1)Centro de Biología Celular y Molecular de Enfermedades, Instituto de Investigaciones Científicas y Servicios de Alta Tecnología de Panamá, Ciudad del Saber, Panamá.
(2)Centro de Biología Celular y Molecular de Enfermedades, Instituto de Investigaciones Científicas y Servicios de Alta Tecnología de Panamá, Ciudad del Saber, Panamá; Universidad Latina de Panamá, Ciudad de Panamá, Panamá.
(3)Caja de Seguro Social, Colón, Panamá.
(4)Programa de Control de Tuberculosis, Ministerio de Salud, Colón, Panamá.
(5)Division of Infectious Diseases & Geographic Medicine, Stanford University, California, United States.
(6)Centro de Biología Celular y Molecular de Enfermedades, Instituto de Investigaciones Científicas y Servicios de Alta Tecnología de Panamá, Ciudad del Saber, Panamá. Electronic address: agoodridge@indicasat.org.pa.

Mycobacterium tuberculosis lineage 2 (L2) remains a globally significant lineage associated with increased drug resistance and rapid transmission. The L2 lineage exhibits a hotspot for genetic diversity and evolution in Panama, requiring an in-depth analysis. We conducted a prospective analysis of 274 Mycobacterium tuberculosis L2 isolates from Colon City between January 2021 and October 2023. Drug resistance was determined using GeneXpert and MTBDRplus-Genotype assays, strain lineage was determined by strain-specific PCR (ASO-PCR), and whole-genome sequencing was conducted for phylogenetic analysis. Sequencing data were analyzed using the mtb-call2 pipeline and TB-gen tools to predict drug resistance and sublineage, respectively. Genome-wide single-nucleotide polymorphisms (SNPs) were used for phylogenetic and evolutionary analyses. ASO-PCR results identified all 31.7 % (86/271) isolates as Modern L2.2. WGS analysis of 66 strains confirmed all isolates belonged to the L2.2.1 sublineage. Sixty-four strains were analyzed in depth, with 96.9 % (62/64) classified as pan-susceptible and 3.1 % (2/64) as rifampicin/pyrazinamide-resistant. The sublineage analysis based on SNPs using the TB-gen tool identified a SNP at position 1219683G > A, which genotyped all 64 strains as L2.2.M3 sublineage.

Phylogenetic analysis revealed a correlation with geographical distribution compared to other Latin American L2 isolates. Transmission clusters (≤12 SNPs) were identified and used to determine recent transmission events or TB transmission clusters. These analyses also confirmed a relatively low evolutionary rate within Panama L2 isolates and a highly conserved common ancestor shared with L2 isolates from Peru, Colombia, and Guatemala. These findings suggest endemic transmission of the Mycobacterium tuberculosis L2.2.M3 sublineage in Colon, Panama. We recommend combining genomic information with epidemiological data to accurately track and identify the source hotspot for the L2.2.M3 sublineage and focus control measures.

DOI: 10.1016/j.meegid.2025.105749
PMID: 40274251 [Indexed for MEDLINE]

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

67. The antibacterial activity and therapeutic potential of the amphibian-derived peptide TB_KKG6K.

mSphere. 2025 Jun 25;10(6):e0101624. doi: 10.1128/msphere.01016-24. Epub 2025 May 19.

Schöpf C(1), Knapp M(2), Scheler J(3), Coraça-Huber DC(4), Romanelli A(5), Ladurner P(2), Seybold AC(2), Binder U(3), Würzner R(3), Marx F(1).

Author information:
(1)Biocenter, Institute of Molecular Biology, Medical University of Innsbruck, Innsbruck, Austria.
(2)Department of Zoology, University of Innsbruck, Innsbruck, Austria.
(3)Institute of Hygiene and Medical Microbiology, Medical University of Innsbruck, Innsbruck, Austria.
(4)Research Laboratory for Implant Associated Infections (BIOFILM LAB), Experimental Orthopaedics, University Hospital for Orthopaedics and Traumatology, Medical University of Innsbruck, Innsbruck, Austria.
(5)Department of Pharmaceutical Sciences, University of Milan, Milan, Italy.

Antimicrobial peptides (AMPs) have great potential to be developed as topical treatments for microbial infections of the skin, including those caused by the gram-positive human pathogen Staphylococcus aureus. Among the AMPs, temporin B (TB) is of particular interest. This 13-amino-acid-long cationic peptide is

secreted by the granular glands of the European frog Rana temporaria and represents a primary line of defense against invading pathogens. The objective of this study was to investigate the antibacterial efficacy and the mode of action of the synthetic TB analog, TB_KKG6K, in a drug-resistant clinical isolate of S. aureus and assess the peptide's tolerance and curative potential in an in vitro infection model using three-dimensional human epidermis equivalents (HEEs). The results revealed a high bactericidal efficacy of TB_KKG6K at low micromolar concentrations. The peptide perturbed the bacterial cell membrane integrity by permeabilization and depolarization. TB_KKG6K showed no toxicity in the invertebrate mini-host model Galleria mellonella and a high level of tolerance when topically applied in HEEs. Importantly, the therapeutic potential of TB_KKG6K was confirmed in HEEs infected with S. aureus. The topical application of TB_KKG6K significantly reduced the bacterial load and lowered the pro-inflammatory response in the infected HEEs. These findings reinforce the antibacterial potential and therapeutic efficacy of TB_KKG6K against S. aureus infection, particularly in the context of a cutaneous infection.IMPORTANCEThe emergence of multidrug-resistant bacteria has rendered the exploration of novel therapeutic treatment strategies a pivotal area of research. Among the most promising candidates are amphibian-derived antimicrobial peptides (AMPs), which are ideal for the development of novel drugs due to their multifaceted mode of action. Extensive studies have been conducted on these peptides over the last decade, resulting in the development of temporin B (TB) peptide analogs that have undergone modifications to their primary sequence. These modified analogs have demonstrated enhanced antibacterial and antifungal efficacy, while exhibiting reduced hemolytic activity. TB_KKG6K has the potential to be a promising candidate for topical treatments due to its small size and high antimicrobial activity against pathogens of the human skin. In particular, it demonstrated efficacy against Staphylococcus aureus, a skin commensal that can become an opportunistic pathogen, causing a range of infections from minor skin infections to life-threatening diseases such as bacteremia and sepsis.

DOI: 10.1128/msphere.01016-24
PMCID: PMC12188738
PMID: 40387366 [Indexed for MEDLINE]

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

68. Intracellular and Extracellular Efficacy of Homoisoflavone Derivatives Against Mycobacterium Tuberculosis: Progress Toward Novel Antitubercular Agents.

ChemMedChem. 2025 Jul 18;20(14):e202500249. doi: 10.1002/cmdc.202500249. Epub 2025 Jun 4.

Calixto SD(1)(2), Falcão JS(3), Antunes SS(4), Araujo MH(1), Cunha ALB(3), Martins DR(3), Nascimento SMR(3), Simão TLBV(2), Lasunskaia EB(2), Romeiro NC(4), Costa PRR(3), Muzitano MF(1), Caleffi GS(3).

Author information:
(1)Laboratório de Produtos Bioativos, Instituto de Ciências Farmacêuticas, Universidade Federal do Rio de Janeiro, Macaé, Rio de Janeiro, 27930-560, Brazil.
(2)Laboratório de Biologia do Reconhecer, Centro de Biociências e Biotecnologia, Universidade Estadual do Norte Fluminense Darcy Ribeiro, Campos dos Goytacazes, Rio de Janeiro, 28013-602, Brazil.
(3)Laboratório de Química Bioorgânica, Instituto de Pesquisas de Produtos Naturais Walter Mors, Universidade Federal do Rio de Janeiro, Rio de Janeiro, 21941-902, Brazil.
(4)Laboratório Integrado de Computação Científica, Instituto Multidisciplinar de Química, Universidade Federal do Rio de Janeiro, Macaé, Rio de Janeiro, 27930-560, Brazil.

Tuberculosis (TB) remains a leading cause of death among infectious diseases globally, necessitating new drug discovery due to rising drug-resistant strains. Homoisoflavones, a distinct subgroup of flavonoids characterized by their 3-benzylidenechroman-4-one skeleton, are promising natural products for new antimicrobials. This study explored 42 homoisoflavone derivatives as potential anti-TB agents. Several derivatives showed potent anti-Mycobacterium tuberculosis (Mtb) activity. Specifically, derivatives 19, 22, and 41 show good selectivity index and significantly inhibited the Mtb H37Rv strain (MIC90 2.2, 3.8, and 1.9 μM, respectively). Derivatives 22 and 41 were particularly effective against the hypervirulent clinical isolate Mtb M299 (MIC90 1.5 and 2.5 μM, respectively), surpassing the potency of rifampicin (MIC90 3.3 μM). Furthermore, these derivatives inhibited intracellular Mtb H37Rv growth in infected macrophages, with derivative 41 proving most potent (IC50 5.2 μM) due to its unique nitrofuranyl and piperidine groups. The study also established a structure-activity relationship (SAR) for the homoisoflavone scaffold. In silico analyses suggest these compounds have good oral bioavailability and low toxicity. These findings highlight homoisoflavone derivatives as promising candidates for future anti-TB drug development.

DOI: 10.1002/cmdc.202500249
PMCID: PMC12276032
PMID: 40354512 [Indexed for MEDLINE]

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

69.Stigmatization and discrimination of female tuberculosis patients in Kyrgyzstan - a phenomenological study.

Int J Equity Health. 2025 Jul 1;24(1):185. doi: 10.1186/s12939-025-02566-4.

Brüggemann R(1)(2), Schlumberger F(3), Chinshailo F(2), Willis M(4), Kadyrov A(2), Kalmambetova G(2), Chen M(1), Unterkircher SC(3)(5), Moidunova N(2), Sydykova A(2), Fastenau A(5)(6).

Author information:
(1)Department of Health Ethics and Society, Faculty of Health, Medicine and Life Sciences, Maastricht University, Maastricht, 6211 LK, The Netherlands.
(2)National Tuberculosis Program Kyrgyzstan (NTP), Akhunbayeva Street 90a, Bishkek, 720020, Kyrgyzstan.
(3)Marie Adelaide Leprosy Center (MALC), Karachi, 74400, Pakistan.
(4)Department of Global Health, Institute of Public Health and Nursing Research, University of Bremen, Bremen, 28359, Germany. willis@uni-bremen.de.
(5)Department of Global Health, Institute of Public Health and Nursing Research, University of Bremen, Bremen, 28359, Germany.
(6)German Leprosy and Tuberculosis Relief Association (GLRA/DAHW), 97080, Wurzburg, Germany.

INTRODUCTION: The Republic of Kyrgyzstan is among the 30 countries with the highest burden of multidrug-resistant Tuberculosis worldwide. One of the reasons is widespread stigmatization and discrimination. As previous research has shown, particularly women experience stigma while its impact on their life and (mental) health is even greater than for men. This is the first phenomenological study to explore women's lived experiences of TB-related stigmatization in Kyrgyzstan. This study aims to raise awareness about the gender-specific impact of stigmatization and discrimination.
METHODOLOGY: Descriptive phenomenology was used. 15 semi-structured in-depth interviews with female TB-patients were conducted between 28th May and 14th June 2024. Themes were stigma experiences, their consequences and coping strategies. Participants were recruited from two TB Hospitals and two Family Medical Centers (primary health care units) in Bishkek through purposive sampling. The data analysis followed a thematic approach based on a combination of deductive and inductive coding.
RESULTS: 14 of 15 participants experienced stigmatization and discrimination in one way or another. Anticipated stigma was very prominent, manifesting in non-disclosure of the diagnosis apart from close family. Enacted stigma mostly occurred within society or non-TB-specialized healthcare facilities. Self-stigmatization often followed anticipated and enacted stigma. Stigma

experiences impacted daily and social life, marital prospects and access to educational and work opportunities but mainly led to mental health issues, which 12 of 15 participants reported.
DISCUSSION: and Conclusion. In contrast to previous research, this study did not find diagnostic delay nor non-adherence to treatment because of stigmatization and discrimination. However, experiences within the healthcare facilities impacted the perceived quality of care. Stigmatization within the family, mostly by in-laws, was anchored in the patriarchal and conservative attitudes of Kyrgyz society. Overall, key findings of this study were widespread lack of knowledge about the disease and its transmission as a reason for and mental health issues because of stigmatization and discrimination. The findings imply the need for intervention strategies and policies focusing on education about TB, integration of psychosocial support into treatment and improvements in quality of care. Altogether, this could contribute to the reduction of TB-related stigmatization and discrimination which would reduce the individual burden of TB.

DOI: 10.1186/s12939-025-02566-4
PMCID: PMC12210680
PMID: 40598484 [Indexed for MEDLINE]

Conflict of interest statement: Declarations. Ethics approval and consent to participate: Local ethical clearance granted by the Ministry of Health, Kyrgyzstan (01–8/14). Additionally, this study has ethical approval from Maastricht University (FHML/GH_2024.022). Consent for publication: All authors read and approved the final manuscript. Competing interests: The authors declare no competing interests.

70. Delayed culture conversion predicts poor outcomes for isoniazid mono-resistant TB in Uganda: a retrospective cross-sectional study from 2017- 2022.

BMC Infect Dis. 2025 Jul 1;25(1):821. doi: 10.1186/s12879-025-11218-5.

Kabugo J(1)(2), Sande OJ(3), Kabahita JM(4), Namutebi J(4), Mujuni D(4), Oundo HR(5), Kisakye D(4), Batte DN(4), Joloba M(4)(3), Mboowa G(3)(6)(7).

Author information:
(1)The WHO Supranational Tuberculosis Reference Laboratory, Ministry of Health, Kampala, Uganda. ksolomonjoel@gmail.com.
(2)Department of Immunology and Molecular Biology, School of Biomedical Sciences, College of Health Sciences, Makerere University, P. O Box 7072, Kampala, Uganda. ksolomonjoel@gmail.com.

(3)Department of Immunology and Molecular Biology, School of Biomedical Sciences, College of Health Sciences, Makerere University, P. O Box 7072, Kampala, Uganda.
(4)The WHO Supranational Tuberculosis Reference Laboratory, Ministry of Health, Kampala, Uganda.
(5)Department of National Health Laboratory and Diagnostic Services, Central Public Health Laboratories, Kampala, Uganda.
(6)African Center of Excellence in Bioinformatics and Data-Intensive Sciences, Infectious Diseases Institute, College of Health Sciences, Makerere University, P.O Box 22418, Kampala, Uganda.
(7)Africa Centres for Disease Control and Prevention, African Union Commission, P.O Box 3243, Roosevelt Street, Addis Ababa, W21 K19, Ethiopia.

BACKGROUND: Isoniazid-resistant, Rifampicin-susceptible Tuberculosis (TB) is estimated to occur in 13% of new cases and 17% of previously treated cases. Current WHO guidelines recommend treatment with Rifampicin (RFP), ethambutol (EMB, E), pyrazinamide (PZA, Z), and levofloxacin (LFX, Q) for 6 months in patients with isoniazid mono-resistant TB (Hr-TB) but the effectiveness and use of other regimens in managing Hr-TB has not been established. There is a need to pay increased attention to the timely identification of Hr-TB patients to improve treatment success along with the reduction of the risk for further drug resistance development. This study was performed to determine the treatment outcomes and their associated factors among isoniazid mono-resistant TB patients in Uganda.
METHODS: This was a cross-sectional study performed among newly diagnosed and retreatment TB patients whose sputum samples were referred to the National TB Reference Laboratory (NTRL)-Uganda from March 2017 to March 2022. Patient samples exhibiting Isoniazid mono-resistance as determined by phenotypic drug resistance testing (DST) were included in this study. Samples with data incompleteness and those whose treatment centers could not be traced were excluded from the study. Selected samples were tested for mutations associated with Isoniazid resistance using line probe. Patient demographic data was obtained from the National TB Reference Laboratory (NTRL) electronic data system and request forms with additional data, such as treatment regimen, adverse effects, and treatment start dates obtained from treatment registers. The independent variables available (age, sex, regimen used, M. tuberculosis mutation genes for isoniazid, specifically InhA and KatG, history of TB, HIV status, and reporting year) were assessed as possible factors in the relationship between Hr-TB and treatment success.
RESULTS: A total of 85 isoniazid monoresistant isolates from different patients were analyzed in this study. In this study, most of the participants belonged to the category of newly diagnosed 35/85 (41.2%). Most of the participants 36/85, 42.3%) turned culture negative at month one upon initiation of treatment. The findings from this study show that the most dominant Mycobacterium tuberculosis

mutation occurred in the KatG MUT1 region with a nucleotide change of S315T1. There was no significant treatment outcome difference among the different age groups in this study when compared (unsuccessful Vs successful treatment, median age 35.4 years and 35.86 years, p = 0.078). However, the study found that most deaths were among people aged above 36 years 71.4%, (5/7 participants). CONCLUSION: This study revealed Isoniazid mono-resistant TB as a significant factor associated with delayed culture conversion of beyond two (2) months. This emphasizes the need for prompt detection using routine point-of-care testing molecular diagnostic platforms to test for Isoniazid and Rifampicin resistance to improve TB treatment outcomes and reduce failures.
CLINICAL TRIAL NUMBER: Not applicable.

DOI: 10.1186/s12879-025-11218-5
PMCID: PMC12210759
PMID: 40597784 [Indexed for MEDLINE]

Conflict of interest statement: Declarations. Ethics approval and consent to participate: The Study was approved by the ethics committee of Makerere School of Biomedical Sciences Research Ethics Committee (SBSREC) under research registration numbers SBS-2022-270. The SBSREC approved a waiver of consent to use stored patient isolates and data for this study to ensure the privacy rights of the patient data used. Administrative approval to access isolates and data of this study was sought from the management of the National Tuberculosis Reference Laboratory. All the data collected for this study was fully anonymized, with no patient name revelations throughout the data collection and analysis phase. Consent for publication: Not applicable. Competing interests: The authors declare no competing interests.

71. Mutations associated with resistance to rifampicin and isoniazid identified in strains of the Mycobacterium tuberculosis complex by GenoType MTBDRplus in Panama, 2015-2021.

Microbiol Spectr. 2025 Jul;13(7):e0240024. doi: 10.1128/spectrum.02400-24. Epub 2025 Jun 9.

Domínguez González J(#)(1), Castillo Mewa J(#)(1), González P(1), Del Cid P(1), Pérez Ruíz JA(1), Rosas Hermosilla SE(1).

Author information:
(1)Instituto Conmemorativo Gorgas de Estudios de la Salud, Panama City, Panama.
(#)Contributed equally

Tuberculosis is one of the diseases causing high rates of morbidity and mortality in several countries. However, efforts in the use of diagnostic methods for tuberculosis and the detection of drug resistance are essential to reduce cases. Since 2015, rapid molecular diagnostic tests have been implemented in Panama, enabling the detection of drug resistance, mainly rifampicin and isoniazid, in patients with suspected tuberculosis. This study aimed to identify mutations in Mycobacterium tuberculosis complex strains with resistance to rifampicin and isoniazid using GenoType MTBDRplus. It is a retrospective study reviewing the results of the GenoType MTBDRplus version 2.0 test from 2015 to 2021. Strains not identified as Mycobacterium tuberculosis complex and those that did not show a mutation pattern and were categorized as sensitive were excluded. Data analysis was carried out using the Chi-square tests, Pearson's Correlation, and principal components analysis. A total of 4,301 strains were analyzed, of which 8.8% were detected with mutation or resistance probes in one or more of the genes analyzed: 56.0% in the rpoβ gene, 11.9% in the inhA gene, and 8.2% in the katG gene. In addition, other mutations such as rpoβ/inhA and rpoβ/katG were detected in 9.5% and 13.5% of cases, respectively. Thirty-eight resistance patterns were identified, with H526D and S531L being the most frequent mutations in the rpoB gene, and S315T1 and C-15T are the most common in katG and inhA, respectively. The resistance patterns detected by the GenoType MTBDRplus assay highlight the genetic variability of drug resistance in the country and emphasize the need to implement epidemiological surveillance methodologies. Integrating patient clinical data with genetic variation information is essential for improving disease control and understanding transmission dynamics and drug resistance acquisition. These findings also provide important insights for guiding tuberculosis treatment strategies in Panama, supporting the use of molecular tools for the early detection of drug resistance, enhancing our understanding of the epidemiology, and informing clinical decision-making.
IMPORTANCE: This study focuses on understanding how Mycobacterium tuberculosis strains in Panama develop resistance. With tuberculosis (TB) cases becoming harder to treat due to drug resistance, especially after the disruptions caused by the COVID-19 pandemic, rapid and accurate diagnosis is crucial. By using advanced molecular tests to identify specific genetic mutations in drug-resistant TB strains, this research helps improve treatment decisions, leading to better outcomes for patients. Understanding these mutations also aids in controlling the spread of TB. Given the rising global concern over drug-resistant TB, the findings of this study are important not only for Panama but also for other regions facing similar challenges.

DOI: 10.1128/spectrum.02400-24
PMCID: PMC12211072
PMID: 40488462 [Indexed for MEDLINE]

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

72. Synthesis, Characterization, and Anti-TB Application of Redox-Active Ethyl Carbazate-Derivatized Phenanthroline and Its Silver Complexes.

ACS Omega. 2025 Jun 13;10(27):28993-29013. doi: 10.1021/acsomega.5c00871. eCollection 2025 Jul 15.

Aluri R(1), Natarajan A(1), Kumari J(2), Sriram D(2), Samanta PK(1), Gangopadhyay A(3), Rangan K(1).

Author information:
(1)Department of Chemistry, Birla Institute of Technology and Science, Pilani, Hyderabad Campus, Jawahar Nagar, Hyderabad 500 078, Telangana, India.
(2)Department of Pharmacy, Birla Institute of Technology and Science, Pilani, Hyderabad Campus, Jawahar Nagar, Hyderabad 500 078, Telangana, India.
(3)Department of Chemical Technology, University of Calcutta, 92 APC Road, Kolkata 700009, West Bengal, India.

Exploring the design and synthesis of new antibiotic compounds is important to treat multidrug-resistant bacterial infections for the already exposed drug molecules. In this work, a phenanthroline derivative, namely, 6-[2-(ethoxycarbonyl)-diazen-1-yl]-1,10-phenanthroline-5-one (ECDPO), and its mono- and bis-ligand silver complexes [Ag-(ECDPO)-(NO3)] and [Ag-(ECDPO)2]-(NO3) were synthesized. Single-crystal X-ray diffraction (XRD) structure of methanol-solvated ECDPO was studied, which crystallized in a monoclinic system, P21/n space group. ECDPO is a planar molecule, and supramolecular arrays are stabilized by various hydrogen bonding, namely, O-H···N, N-H···O, and C-H···O, and π-π interactions. The spectroscopic features of ECDPO and its silver complexes were thoroughly studied by high-resolution mass spectrometry (HRMS), IR, 1H NMR, 13C NMR, UV-visible spectroscopy, and X-ray photoelectron spectroscopy (XPS). Electrochemical redox features were studied by cyclic voltammetry. The ECDPO molecule and its silver complexes were studied for antibacterial activity against bacteria and (Mtb). ECDPO shows a minimum inhibitory concentration (MIC) of 1.56 μg/mL against Mtb, which is comparable to that of one of the clinically used drug candidates, namely, ethambutol. Silver complexes [Ag-(ECDPO)-(NO3)] and [Ag-(ECDPO)2]-(NO3) showed enhanced anti-TB activities and MICs of 0.78 and 0.39 μg/mL, respectively.

DOI: 10.1021/acsomega.5c00871

PMCID: PMC12273601
PMID: 40687003

73. Insights into anti-tuberculosis drug design on the scaffold of nitroimidazole derivatives using structure-based computer-aided approaches.

RSC Adv. 2025 Jul 3;15(28):22745-22763. doi: 10.1039/d5ra01362c. eCollection 2025 Jun 30.

Yang W(1)(2)(3), Zhao H(1)(2), Zhao Z(1)(2), Pei S(4)(5)(6), Zhu Z(7), Huang Z(1)(2), Zhao Y(1)(2), Lu S(1)(2), Wang F(8), Zhao Y(1)(2)(5)(6).

Author information:
(1)National Clinical Research Center for Infectious Diseases, Shenzhen Third People's Hospital Shenzhen 518112 China.
(2)Shenzhen Clinical Research Center for Tuberculosis Shenzhen People's Republic of China.
(3)Warshel Institute for Computational Biology, School of Science and Engineering, The Chinese University of Hong Kong Shenzhen 518172 China.
(4)Department of Global Health, School of Public Health, Peking University Beijing 100191 China.
(5)National Center for TB Control and Prevention, Chinese Center for Disease Control and Prevention Beijing 102206 China zhaoyl@chinacdc.cn.
(6)Chinese Center for Disease Control and Prevention Beijing 102206 China.
(7)Department of Urology, Xijing Hospital, Air Force Military Medical University Xi'an China.
(8)School of Life Science, Linyi University Linyi 276000 China.

Deazaflavin-dependent nitroreductase (Ddn) is a crucial enzyme involved in mycolic acid biosynthesis, a vital component of the cell wall in Mycobacterium tuberculosis (MTB)-the bacterial pathogen responsible for tuberculosis. Over the past two decades, nitroimidazole oxazine scaffold (NOS) derivatives have been investigated as potential therapeutic agents targeting Ddn in MTB, with a focus on enhancing drug efficacy, minimizing toxicity, and combating drug resistance. In this study, we performed an extensive theoretical investigation combining three-dimensional quantitative structure-activity relationship (3D-QSAR) studies, all-atom molecular docking, and atomic-level molecular dynamics (MD) simulations. Additionally, we analyzed the binding free energies and their decomposed terms between inhibitors and Ddn to elucidate the structure-activity relationships (SARs) and mechanisms of a series of NOS derivatives developed for MTB inhibition. The CoMFA and CoMSIA models demonstrated strong performance, with cross-validation coefficients (R cv 2) of 0.591 and 0.629, respectively, and prediction coefficients (R pred 2) of 0.7698 and 0.6848 for CoMFA and

CoMSIA, respectively. These models effectively predicted the minimum inhibitory concentration (MIC) values of the compounds against MTB based on the NOS scaffold. Molecular docking followed by MD simulations was employed to validate the binding modes of these derivatives at the active site of Ddn, providing detailed insights into their interaction patterns. Notably, our analysis revealed that residues Tyr65, Ser78, Tyr130, Tyr133, and Tyr136 played critical roles in determining the potency of the compounds by contributing significantly to their binding energies. These findings provide valuable guidance for the rational design of novel NOS inhibitors with enhanced potential as effective anti-tuberculosis agents.

DOI: 10.1039/d5ra01362c
PMCID: PMC12224256
PMID: 40612639

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

74. Structural and functional analysis of the Mycobacterium tuberculosis MmpS5L5 efflux pump presages a pathway to increased bedaquiline resistance.

bioRxiv [Preprint]. 2025 Jun 24:2025.06.24.661325. doi: 10.1101/2025.06.24.661325.

Fountain AJ, Böhning J, McLaughlin SH, Morgan TE, Edelstein PH, Troll M, Lamers MH, Bharat TAM, Luisi BF, Ramakrishnan L.

Bedaquiline, an antitubercular drug that targets ATP-synthase, is a key component of a new oral drug regimen that has revolutionized the treatment of multi drug resistant tuberculosis. Clinical bedaquiline resistance in Mycobacterium tuberculosis has rapidly emerged, primarily due to mutations in the transcriptional repressor, Rv0678 that result in upregulation of the Resistance-Nodulation-Division (RND) efflux pump MmpS5/MmpL5 (MmpS5L5). Here, to understand how MmpS5L5 effluxes bedaquiline, we determined the structure of the MmpS5L5 complex using cryo-electron microscopy, revealing a novel trimeric architecture distinct from the canonical tripartite RND efflux pumps of Gram-negative bacteria. Structure prediction modelling in conjunction with functional genetic analysis indicates that it uses a periplasmic coiled-coil tube to transport molecules across the cell wall. Structure-guided genetic approaches identify MmpL5 mutations that alter bedaquiline transport; these mutations converge on a region in MmpL5 located in the lower portion of the

periplasmic cavity, proximal to the outer leaflet of the inner membrane, suggesting a route for bedaquiline entry into the pump. While currently known clinical resistance to bedaquiline is due to pump upregulation, our findings that several MmpL5 variants increase bedaquiline efflux may presage the emergence of additional modes of clinical resistance.
SIGNIFICANCE STATEMENT: Resistance to bedaquiline, a cornerstone drug for treating multidrug-resistant tuberculosis, is rapidly emerging due to mutations that upregulate expression of the MmpS5L5 efflux pump. Here, we reveal the cryo-EM structure of this pump, showing a novel trimeric architecture and a unique α-helical coiled-coil tube for drug transport. Structure-guided genetic analysis identifies MmpL5 variants that further increase bedaquiline efflux, suggesting potential resistance mechanisms beyond pump upregulation.

DOI: 10.1101/2025.06.24.661325
PMCID: PMC12262577
PMID: 40667120

75. Establishing the Exposure-QT Relationship During Bedaquiline Treatment Using a Time-Varying Tuberculosis-Specific Correction Factor (QTcTBT).

CPT Pharmacometrics Syst Pharmacol. 2025 Jul;14(7):1252-1261. doi: 10.1002/psp4.70047. Epub 2025 May 14.

Vongjarudech T(1), Dosne AG(2), Remmerie B(2), Karlsson MO(1), Svensson EM(1)(3).

Author information:
(1)Department of Pharmacy, Uppsala University, Uppsala, Sweden.
(2)Janssen R&D, Beerse, Belgium.
(3)Department of Pharmacy, Pharmacology and Toxicology, Radboud University Medical Center, Nijmegen, the Netherlands.

Evaluating QT prolongation induced by anti-tuberculosis (TB) drugs in patients with active TB, who often experience tachycardia, is challenging due to the limitations of Fridericia's correction factor (QTcF) in decorrelating QTc from heart rate (HR). Previous exposure-QTcF analyses in patients with active TB were able to alleviate the limitation of QTcF but required advanced model-based methodologies, incorporating a non-drug-related, "secular" trend in the model to dissociate drug and non-drug-related effects on QT. Recently, we developed and validated a time-varying QT correction method (QTcTBT) that more accurately accounts for the HR changes during TB treatment. In the present work, using data from 429 patients with multidrug-resistant TB across two Phase IIb trials, we re-evaluated the exposure-QTc relationship for bedaquiline by applying QTcTBT

instead of QTcF. Our analysis showed that when HR changes were accounted for using QTcTBT, a typical maximum M2 (bedaquiline metabolite) concentration (326 ng/mL, mean maximal concentration (Cmax) at the end of 2-week loading phase) was associated with a 7 ms QTc interval prolongation (90% CI: 5.9-8.2). This estimate closely aligns with the previously reported M2 effect of 7.9 ms (90% CI: 6.8-9.3), derived from the exposure-QTcF model. The consistency between the two methodologies further supports the use of QTcTBT for estimating the QTc prolongation effects of anti-TB drugs.

DOI: 10.1002/psp4.70047
PMCID: PMC12256558
PMID: 40369885 [Indexed for MEDLINE]

Conflict of interest statement: A.G.D. and B.R. are employed by Janssen. All other authors declared no competing interests for this work.

76. High-Level Primary Pretomanid-Resistant with ddn In-Frame Deletion of and Its Association with Lineage 4.5 in China.

ACS Omega. 2025 Jun 23;10(25):26551-26559. doi: 10.1021/acsomega.5c00610. eCollection 2025 Jul 1.

Pei S(1)(2), Yang W(3)(4), Ou X(5)(6), Zhao B(5)(6), Zhao Z(7), Wang Z(1), Song Z(5)(6), Wang S(5)(6), Zhuang J(4), Li C(8), Zhao Y(5)(6).

Author information:
(1)Department of Global Health, School of Public Health, Peking University, Beijing 100191, China.
(2)Division of General Internal Medicine and Primary Care, Brigham and Women's Hospital, Boston, Massachusetts 02120, United States.
(3)National Clinical Research Center for Infectious Diseases, Shenzhen Third People's Hospital, Shenzhen 518112, China.
(4)Warshel Institute for Computational Biology, School of Life and Health Sciences, School of Medicine, The Chinese University of Hong Kong, Shenzhen 518172, China.
(5)National Center for TB Control and Prevention, Chinese Center for Disease Control and Prevention, Beijing 102206, China.
(6)National Key Laboratory of Intelligent Tracking and Forecasting for Infectious Diseases, Chinese Center for Disease Control and Prevention, Beijing

102206, China.
(7)School of Basic Medical Sciences, Tianjin Medical University, Tianjin 300070, China.
(8)Biomedicine Discovery Institute and Department of Biochemistry and Molecular Biology, Monash University, Melbourne, Victoria 3800, Australia.

Pretomanid (PMD) is a key antibiotic of the newest multidrug-resistant or rifampicin-resistant tuberculosis treatment regimen "BPaL", but knowledge of its resistance mutations is still limited, especially in China, as it was approved only in late 2024. We analyzed a collection of (MTB) isolates from China including the whole-genome sequencing and drug susceptibility testing data and extended analysis to other 2165 isolates from lineage 4. We found in-frame deletion variants in the ddn genome sequence in the isolates collected in Xinjiang Uyghur Autonomous Region, China, with a high level of PMD resistance without pre-exposure to PMD belonging to sublineage 4.5. The extended analysis found that in-frame deletion variants occurred more frequently in sublineage 4.5. Some isolates contain multiple ancestral components after historical evolution, which may cause in-frame deletion variants to spread in some settings. Furthermore, molecular dynamics simulations and free energy calculations of the key mutants indicated that the impaired mutant structures result in unfavorable domination binding, which poses less probability for PMD activation for targeting other critical MTB targets and also leads to insufficient generation of NO (nitric oxide) to kill MTB. Currently, PMD resistance is mainly due to ddn gene mutations, especially frameshift mutations. However, our findings underscore the importance of surveillance for in-frame deletions, especially in regions with a high prevalence of sublineage 4.5, and the high level of PMD resistance conferred by deletions raises crucial concerns about the future effectiveness of the BPaL regimen.

DOI: 10.1021/acsomega.5c00610
PMCID: PMC12235975
PMID: 40630726

77. A cytoderm metabolic labeling TPAPy-Tre for real-time detection of vitality of Mycobacterium tuberculosis in sputum.

Microbiol Spectr. 2025 Jul;13(7):e0245724. doi: 10.1128/spectrum.02457-24. Epub 2025 May 22.

Yang M(#)(1)(2), Dai G(#)(3), Li D(#)(4), Zhao P(3), Zhan S(5), Qin H(5), Lu H(6), Zheng M(2), Zhang P(1)(2)(5).

Author information:
(1)School of Public Health, Shenzhen University Medical School, Shenzhen University, Shenzhen, Guangdong, China.
(2)Shenzhen Clinical Research Center for Tuberculosis, Shenzhen, China.
(3)Institute of Hepatology, National Clinical Research Center for Infectious Diseases, Third People's Hospital of Shenzhen, Shenzhen, Guangdong, China.
(4)National Clinical Research Center for Infectious Diseases, Shenzhen Clinical Research Center for Tuberculosis, Shenzhen Third People's Hospital, Shenzhen, Guangdong, China.
(5)Department of Pulmonary Medicine and Tuberculosis, Third People's Hospital of Shenzhen, Shenzhen, Guangdong, China.
(6)Department of Infectious Diseases, National Clinical Research Center for Infectious Diseases, Third People's Hospital of Shenzhen, Shenzhen, Guangdong, China.
(#)Contributed equally

Early bactericidal activity is a vital measure in developing new tuberculosis (TB) drugs. Traditional methods, including colony-forming units (CFUs) and time to positivity (TTP), have limitations. This study aimed to evaluate the efficacy of TPAPy-Tre fluorescence microscopy in monitoring early therapeutic responses compared with conventional culture methods in patients with pulmonary multidrug-resistant/rifampicin-resistant TB. In an open-label clinical trial at the Third People's Hospital of Shenzhen, China, seven sputum smear-positive patients aged ≥18 years were enrolled. Sputum samples were consecutively analyzed using solid and liquid cultures and TPAPy-Tre microscopy. The study found that TPAPy-Tre fluorescence intensity significantly decreased from 271.5 (95% confidence interval [CI], 177.4-365.7) before treatment to 142.8 (95% CI, 104.7-180.9) after treatment ($P < 0.05$). TPAPy-Tre results strongly correlated with CFU (Spearman $\rho = 0.60$; 95% CI, 0.35-0.77; $P < 0.001$) and TTP (Spearman $\rho = -0.33$; 95% CI, -0.56 to -0.04; $P < 0.05$). Among selected participants, the median fluorescence intensity decreased from 51.5 (interquartile range [IQR], 39.0-63.6) to 13.2 (IQR, 7.8-20.0) after treatment ($P < 0.001$). TPAPy-Tre shows potential as a rapid, visual method for tracking bacterial vitality during TB treatment, offering immediate feedback on treatment response. These results support its use alongside conventional methods in clinical settings, though larger studies are needed for further validation.IMPORTANCEEarly bactericidal activity (EBA) is an important tool in clinical studies in the development of new tuberculosis drugs. Current traditional methods of efficacy monitoring present significant limitations. There is a need for novel and efficient tools to monitor treatment response in real-time when EBA is performing.

DOI: 10.1128/spectrum.02457-24
PMCID: PMC12211060

PMID: 40401971 [Indexed for MEDLINE]

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

78. In vitro phytochemical, antioxidant activity and antimycobacterial potentials of selected medicinal plants commonly used for respiratory infections and related symptoms in the Limpopo Province, South Africa.

BMC Complement Med Ther. 2025 Jul 9;25(1):248. doi: 10.1186/s12906-025-05002-w.

Matlala MS(1), Moganedi KLM(1), Masoko P(2).

Author information:
(1)Department of Biochemistry, Microbiology and Biotechnology, Faculty of Science and Agriculture, University of Limpopo, Private Bag X1106, Sovenga, 0727, South Africa.
(2)Department of Biochemistry, Microbiology and Biotechnology, Faculty of Science and Agriculture, University of Limpopo, Private Bag X1106, Sovenga, 0727, South Africa. Peter.Masoko@ul.ac.za.

BACKGROUND: The emergence of drug resistance among Mycobacterium tuberculosis (Mtb) strains, coupled with the detrimental side effects linked to tuberculosis (TB) treatment, underscores the persistence of TB as a significant clinical and public health concern in South Africa, thereby necessitating ongoing research in drug discovery. The use of medicinal plants for the treatment of TB has garnered increasing attention, especially in countries where a significant portion of the population relies on traditional medicine as a primary form of healthcare.
METHODS: The crude extracts from nine medicinal plants were investigated for antimycobacterial activity. Phytochemical profiling and qualitative antioxidant activity were assessed using thin layer chromatography. The 2,2-Diphenyl-1-picrylhydrazyl radical scavenging assay was used for quantitative antioxidant analysis. The broth microdilution assay was used to determine the antimycobacterial activity of the plant extracts and rifampicin against Mycobacterium smegmatis (ATCC 1441). Sodium dodecyl polyacrylamide gel electrophoresis was used to qualitatively evaluate the protein profile of M. smegmatis. The growth response of M. smegmatis to both inhibitors (rifampicin and plants extracts) was assessed through growth kinetics assays.
RESULTS: Phytochemical profiling revealed that all plants contained various phytoconstituents in differing concentrations. Additionally, the plants exhibited relatively low antioxidant activity, as indicated by their IC50 values. Rosmarinus officinalis and Zanthoxylum capense demonstrated inhibitory effects on the growth of M. smegmatis with a minimum inhibitory concentration of 0.625 mg/ml. The time-kill assays indicate that the plant extracts including

those of Gardenia volkensii, Citrus lemon, Croton gratissimus and Clerodendrum glabrum exhibited greater growth reduction than rifampicin. Sodium dodecyl polyacrylamide gel electrophoresis profiles revealed distinct patterns of M. smegmatis proteins. Protein profiles suggest that plant extracts, like rifampicin, affect bacterial protein synthesis.
CONCLUSION: The results of this study indicate that the plants do not have potent free radical scavenging capabilities. Nevertheless, they exhibited antimycobacterial properties, notably impacting protein synthesis.

DOI: 10.1186/s12906-025-05002-w
PMCID: PMC12243302
PMID: 40635022 [Indexed for MEDLINE]

Conflict of interest statement: Declarations. Ethics approval and consent to participate: The study was ethically cleared by the Turfloop Research and Ethics Committee (TREC/604/2022: PG). Consent for publication: Not Applicable. Competing interests: The authors declare no competing interests.

79. Development and optimization of an injectable in-situ gel system for sustained release of anti-tuberculosis drugs.

Sci Rep. 2025 Jul 1;15(1):21383. doi: 10.1038/s41598-025-05644-3.

Balu P(1), Srikanth S(2), Gnandhas DP(3), Durai RD(4), Ulaganathan V(2), B Narayanan VH(5).

Author information:
(1)Pharmaceutical Technology Laboratory, School of Chemical and Biotechnology, SASTRA Deemed University, Thanjavur, Tamil Nadu, India.
(2)Molecular Motors Laboratory, Department of Biotechnology, SASTRA Deemed University, Thanjavur, Tamil Nadu, India.
(3)Department of Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE, USA.
(4)Pharmaceutical Technology Laboratory, School of Chemical and Biotechnology, SASTRA Deemed University, Thanjavur, Tamil Nadu, India. ramya@scbt.sastra.edu.
(5)Pharmaceutical Technology Laboratory, School of Chemical and Biotechnology, SASTRA Deemed University, Thanjavur, Tamil Nadu, India. vedhahari@scbt.sastra.edu.

Addressing the challenges of drug-resistant Mycobacterium tuberculosis requires regular drug intake and consistent therapeutic drug concentrations, for which

in-situ gel systems offer a promising solution by enabling sustained drug release. This study aims to develop an injectable system for chronic tuberculosis treatment, focusing on an in-situ gel formulation created using Poloxamer 407, Carbopol 940, and Hydroxy Propyl Methyl Cellulose (HPMC). The experiments involved a combination of two FDA-approved first-line anti-TB molecules, namely Rifampicin (RIF) and Isoniazid (INZ), by loading in the in-situ gel (IGS) formulations prepared by cold process. The gelling polymers were varied at three levels of concentration and optimized through the molecular docking method, wherein the blend of polymers with drugs showed the docking score of - 3.085. The physicochemical properties and analytical characterization, including gelation temperature, drug content, FT-IR, SEM, TG-DSC, in-vitro drug release, ex-vivo permeation, and cytotoxicity, were performed. According to the study results, the optimized gelation temperature was 26 °C, the viscosity of the sol and gel was 238 cP and 1700 cP, respectively, with the maximum drug content (RIF 100 ± 2.17% and INZ 97 ± 1.31%). The FTIR analysis confirmed the stability of drugs, the morphological study using SEM showed the formation of a network structure, and thermal analysis by TG-DSC confirmed the solid-state transition of drugs. The in-vitro drug release studies in phosphate buffer pH 7.4 showed sustained release of Rifampicin and Isoniazid for up to 10 days and 6 days, respectively. The selected formulation exhibited non-toxic effects in the L929 cell line. Based on the results, in-situ gel administration could be recommended for intramuscular administration for sustained release of the drugs, which is expected to reduce the dosing frequency and improve patient compliance for chronic tuberculosis therapy.

DOI: 10.1038/s41598-025-05644-3
PMCID: PMC12215346
PMID: 40595921 [Indexed for MEDLINE]

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

80. Machine learning-based prediction of antimicrobial resistance and identification of AMR-related SNPs in Mycobacterium tuberculosis.

BMC Genom Data. 2025 Jul 12;26(1):48. doi: 10.1186/s12863-025-01338-x.

Xu Y(#)(1)(2), Mao Y(#)(3)(2), Hua X(1)(4), Jiang Y(1)(4), Zou Y(2), Wang Z(2), Liu Z(1)(2), Zhang H(5), Lu L(6), Yu Y(7)(8).

Author information:
(1)Department of Infectious Diseases, Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang, 310016, China.
(2)Key Laboratory of Digital Technology in Medical Diagnostics of Zhejiang Province, Dian Diagnostics Group Co, Ltd, Hangzhou, 310030, China.
(3)Institute of Translational Medicine, Zhejiang University School of Medicine, Hangzhou, Zhejiang, 310029, China.
(4)Key Laboratory of Microbial Technology and Bioinformatics of Zhejiang Province, Hangzhou, 310016, China.
(5)Department of Clinical Laboratory, Zhejiang Hospital, Hangzhou, Zhejiang, 310013, China.
(6)Key Laboratory of Digital Technology in Medical Diagnostics of Zhejiang Province, Dian Diagnostics Group Co, Ltd, Hangzhou, 310030, China. lull1@dazd.cn.
(7)Department of Infectious Diseases, Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang, 310016, China. yvys119@zju.edu.cn.
(8)Key Laboratory of Microbial Technology and Bioinformatics of Zhejiang Province, Hangzhou, 310016, China. yvys119@zju.edu.cn.
(#)Contributed equally

BACKGROUND: Mycobacterium tuberculosis (MTB) is a human-specific pathogen that primarily infects humans, causing tuberculosis (TB). Antimicrobial resistance (AMR) in MTB presents a formidable challenge to global health. The employment of machine learning on whole-genome sequencing data (WGS) presents significant potential for uncovering the genomic mechanisms underlying drug resistance in MTB.
METHODS: We used 18 binary matrices, each consisting of genotypes and antimicrobial susceptibility testing phenotypes from a specific MTB-antimicrobial dataset. By constructing training and test datasets on all SNPs, intersected SNPs, and randomly generated SNPs, we developed a Machine learning (ML) framework using twelve different algorithms. Then, we compared the performances of the various ML models and used the SHapley Additive exPlanations (SHAP) framework to decipher why and how decisions are made within the optimal algorithm. Lastly, we applied the models to predict the resistance phenotype to rifampicin (RIF) and isoniazid (INH) in the additional independent MTB isolate datasets from India and Israel.
RESULTS: In our study, the Gradient Boosting Classifier (GBC) model was the best in terms of correctly identified percentages (97.28%, 96.06%, 94.19%, and 92.81% for the four first-line drugs, RIF, INH, pyrazinamide, and ethambutol respectively). By estimating the contributions of AMR-related SNPs by SHAP values, we found that position 761,155 (rpoB_p.Ser450), 2,155,168 (katG_p.Ser315) rank top in RIF and INH, their higher values (1 for alternative allele) tend to predict the resistance trait for these two drugs. In addition,

the best model GBC generalizes well in predicting the resistance phenotypes for RIF and INH in the external independent MTB isolate datasets from India and Israel.
CONCLUSIONS: This study integrates ML methods into antimicrobial resistance research, develops a framework for predicting resistance phenotypes, and explores AMR-related SNPs in MTB. Quantifying the important SNPs' contribution to model decisions makes the ML algorithmic process more transparent, interpretable enabling and enables clinical practice.

DOI: 10.1186/s12863-025-01338-x
PMCID: PMC12255030
PMID: 40646483 [Indexed for MEDLINE]

Conflict of interest statement: Declarations. Ethics approval and consent to participate: Not applicable. Consent for publication: Not applicable. Competing interests: The authors declare no competing interests.

81. FuNTB: a functional network clustering tool for the analysis of genome-wide genetic variants in Mycobacterium tuberculosis.

Bioinformatics. 2025 Jul 1;41(7):btaf341. doi: 10.1093/bioinformatics/btaf341.

Ramos-García AA(1), Mejía-Ponce PM(2), Sélem-Mojica N(3), Santos-Díaz A(1), Martínez-Ledesma E(4)(5), Licona-Cassani C(2)(4)(6).

Author information:
(1)Escuela de Ingeniería y Ciencias, Tecnológico de Monterrey, Monterrey, Nuevo León, 64700, México.
(2)Centro de Biotecnología FEMSA, Escuela de Ingeniería y Ciencias, Tecnológico de Monterrey, Monterrey, Nuevo León, 64700, México.
(3)Centro de Ciencias Matemáticas, Universidad Nacional Autónoma de México, Residencial San José de la Huerta, Morelia, Michoacán, 58089, México.
(4)Unidad de Biología Integrativa, The Institute for Obesity Research, Tecnológico de Monterrey, Monterrey, Nuevo León, 64700, México.
(5)Escuela de Medicina y Ciencias de la Salud, Tecnológico de Monterrey, Monterrey, Nuevo León, 64700, México.
(6)Instituto de Biotecnología, Universidad Nacional Autónoma de México, Cuernavaca, Morelos, 62210, Mexico.

MOTIVATION: Tuberculosis (TB), caused by Mycobacterium tuberculosis (Mtb), still claims around 1.25 million lives each year. The growing threat of drug

resistance-often driven by single-nucleotide polymorphisms (SNPs) in Mtb genomes underscores the need for high-quality genomic data and powerful bioinformatics tools. We present FuNTB, a python-based pipeline that detects non-synonymous SNPs in Mtb and builds functional network clusters to reveal genotype-phenotype relationships.
RESULTS: FuNTB profiles non-synonymous SNPs at the gene level across user-defined phenotypes, pinpointing both shared and unique mutations. It ingests annotated Variant Call Format (VCF) files or MTBseq outputs and merges them with clinical metadata to produce network-XML files compatible with Cytoscape and Gephi. When applied to the CRyPTIC Mtb collection, FuNTB rapidly recovered established resistance genes and surfaced novel candidates, validating its utility for mapping genotype-phenotype associations.
AVAILABILITY AND IMPLEMENTATION: FuNTB is implemented in Python 3.8+ and is freely available under the MIT license at https://doi.org/10.5281/zenodo.15399917.

DOI: 10.1093/bioinformatics/btaf341
PMCID: PMC12255883
PMID: 40498551 [Indexed for MEDLINE]

82. Leveraging large language models to predict antibiotic resistance in Mycobacterium tuberculosis.

Bioinformatics. 2025 Jul 1;41(Supplement_1):i40-i48. doi: 10.1093/bioinformatics/btaf232.

Testagrose C(1), Pandey S(1), Serajian M(1), Marini S(2), Prosperi M(2), Boucher C(1).

Author information:
(1)Department of Computer and Information Science and Engineering, University of Florida, Gainesville, FL 32611, United States.
(2)Department of Epidemiology, University of Florida, Gainesville, FL 32601, United States.

MOTIVATION: Antibiotic resistance in Mycobacterium tuberculosis (MTB) poses a significant challenge to global public health. Rapid and accurate prediction of antibiotic resistance can inform treatment strategies and mitigate the spread of resistant strains. In this study, we present a novel approach leveraging large language models (LLMs) to predict antibiotic resistance in MTB (LLMTB). Our model is trained and evaluated on genomic data from 12 185 CRyPTIC isolates and

their associated resistance profiles, utilizing natural language processing techniques to capture patterns and mutations linked to resistance. The model's architecture integrates state-of-the-art transformer-based LLMs, enabling the analysis of complex genomic sequences and the extraction of critical features relevant to antibiotic resistance.
RESULTS: We evaluate our model's performance using a comprehensive dataset of MTB strains, demonstrating its ability to achieve high performance in predicting resistance to various antibiotics. Unlike traditional machine learning methods, fine-tuning or few-shot learning opens avenues for LLMs to adapt to new or emerging drugs, thereby reducing reliance on extensive data curation. Beyond predictive accuracy, LLMTB uncovers deeper biological insights, identifying critical genes, intergenic regions, and novel resistance mechanisms. This method marks a transformative shift in resistance prediction and offers significant potential for enhancing diagnostic capabilities and guiding personalized treatment plans, ultimately contributing to the global effort to combat tuberculosis and antibiotic resistance.
AVAILABILITY AND IMPLEMENTATION: All source code is publicly available at https://github.com/ctestagrose/LLMTB.

DOI: 10.1093/bioinformatics/btaf232
PMCID: PMC12261485
PMID: 40662835 [Indexed for MEDLINE]

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

83. Unpacking bedaquiline heteroresistance: the importance of intermediate profiles for phenotypic drug susceptibility testing.

Antimicrob Agents Chemother. 2025 Jul 21:e0035625. doi: 10.1128/aac.00356-25. Online ahead of print.

Ismail N(#)(1), Sirgel F(#)(1), Omar SV(2), Omar S(1), de Kock M(1), Spies C(1), Folkerts M(3), Theron G(1), Engelthaler D(3), Metcalfe J(#)(4), Warren RM(#)(1).

Author information:
(1)South African Medical Research Council Centre for Tuberculosis Research, Division of Molecular Biology and Human Genetics, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa.
(2)Centre for Tuberculosis, National Institute for Communicable Diseases,

Johannesburg, South Africa.
(3)Translational Genomics Research Institute (TGen) North Clinical Laboratory, Flagstaff, Arizona, USA.
(4)University of California-San Francisco, San Francisco, California, USA.
(#)Contributed equally

Phenotypic drug susceptibility testing (pDST) remains a widely used standard for determination of resistance for several drugs for the Mycobacterium tuberculosis complex. Next-generation sequencing technologies can identify heteroresistant populations at low frequencies, but little is known about the impact of heteroresistance on bedaquiline (BDQ) pDST results. We simulated heteroresistance using in vitro-generated MmpR5 mutants mixed with the progenitor strain at various percentages (1%-20%) and performed pDST using the BACTEC MGIT 960 platform (1 and 2 µg/mL BDQ concentrations) coupled with EpiCenter TB-eXtended individual drug Susceptibility Testing software. Targeted next-generation sequencing was used to quantify the mutant subpopulation in growth control tubes, which were expected to maintain the mutant: wild-type proportion throughout the assay. Growth units of these growth control tubes were also comparable with minor differences in time to positivity between ratio mixtures. Only when intermediate results were considered (i.e., when growth units in a drug-containing tube reach the threshold for resistance but only after a further week of incubation) could BDQ heteroresistance be detected at frequencies of approximately 1% by pDST at a critical concentration of 1 µg/mL. These intermediate results, commonly disregarded during routine testing, could lead to earlier detection of BDQ resistance and may avert adverse clinical outcomes. The ability of pDST, a widely available DST technique, to reveal the presence of BDQ-resistant subpopulations at the phenotypic testing stage could improve resistance determination and potentially reduce time to effective treatment.

DOI: 10.1128/aac.00356-25
PMID: 40689761

84. Baeyer-Villiger monooxygenase immobilized on magnetic nanoparticles: reusable biocatalytic system for drug metabolite synthesis.

Int J Biol Macromol. 2025 Jun 25;319(Pt 3):145588. doi: 10.1016/j.ijbiomac.2025.145588. Online ahead of print.

De Angelis M(1), Liyanage USG(1), Marucco AMB(1), Catucci G(1), Schwaminger SP(2), Gilardi G(3), Sadeghi SJ(4).

Author information:

(1)Department of Life Sciences and Systems Biology, University of Torino, via Accademia Albertina 13, 10123 Torino, Italy.
(2)Division of Medicinal Chemistry, Otto Loewi Research Center, Medical University of Graz, Neue Stiftingtalstraße 6, 8010 Graz, Austria; BioTechMed-Graz, Mozartgasse 12, 8010 Graz, Austria.
(3)Department of Life Sciences and Systems Biology, University of Torino, via Accademia Albertina 13, 10123 Torino, Italy; Nanomaterials for Industry and Sustainability Center, University of Torino, via Accademia Albertina 13, 10123 Torino, Italy.
(4)Department of Life Sciences and Systems Biology, University of Torino, via Accademia Albertina 13, 10123 Torino, Italy; Nanomaterials for Industry and Sustainability Center, University of Torino, via Accademia Albertina 13, 10123 Torino, Italy. Electronic address: sheila.sadeghi@unito.it.

Drug metabolites are critical for assessing drug efficacy, pharmacokinetics, and safety. Biocatalysis offers a selective and sustainable route to their synthesis. In this study, a Baeyer-Villiger monooxygenase from Acinetobacter radioresistens (Ar-BVMO) was immobilized onto bare iron oxide nanoparticles (BIONs), producing a reusable biocatalytic system (BVMO@BION) for drug metabolite production. The magnetic properties of BIONs facilitated easy recovery and reuse of the biocatalyst, making the system practical for repeated use. High loading efficiency (0.14 mg enzyme per mg of BIONs) was achieved through histidine-tag-mediated binding. The immobilized enzyme exhibited enhanced thermostability, increasing its melting temperature from 46.3 °C to 54.9 °C, and reduced nanoparticle aggregation. The system demonstrated robust activity for Baeyer-Villiger and S/N-oxidation reactions. Notably, BVMO@BION achieved over 95 % conversion efficiency for the N-oxidation of tozasertib (an anti-cancer drug) across nine reaction cycles (2 h each) over 3 days, while activity recovery values ranged from 81 % to 127 %. For S-oxidation of ethionamide (an antibiotic used in multidrug-resistant tuberculosis) approximately 26 % conversion was consistently achieved across eight 1-hour cycles. This work demonstrates that BVMO@BION is a robust, magnetically recoverable platform for repeated and selective drug metabolite synthesis, supporting greener and more efficient pharmaceutical development.

DOI: 10.1016/j.ijbiomac.2025.145588
PMID: 40578651

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.

85. Impact of the COVID-19 pandemic on unfavorable tuberculosis outcomes: a comparative analysis of unhoused and general populations.

BMC Public Health. 2025 Jul 2;25(1):2260. doi: 10.1186/s12889-025-23491-9.

da Silva Campana P(1), da Silva ATC(2), Klautau GB(2), Rujula MJP(2), Salles MJ(2)(3), de Castro MC(4).

Author information:
(1)Faculdade de Ciências Médicas da Santa Casa de São Paulo, R. Dr. Cesário Mota Júnior, 61 - Vila Buarque, São Paulo, 01225-070, SP, Brasil. pedro.campana@fcmsantacasasp.edu.br.
(2)Faculdade de Ciências Médicas da Santa Casa de São Paulo, R. Dr. Cesário Mota Júnior, 61 - Vila Buarque, São Paulo, 01225-070, SP, Brasil.
(3)Laboratório Especial de Microbiologia Clínica, Universidade Federal de São Paulo, R. Sena Madureira, 1500 - Vila Clementino, São Paulo, 04021-001, SP, Brasil.
(4)Harvard T.H. Chan School of Public Health, 677 Huntington Ave, Boston, MA, 02115, USA.

INTRODUCTION: Tuberculosis care has been seriously affected by the COVID-19 pandemic. Few studies have assessed the impact of the pandemic on tuberculosis outcomes in vulnerable populations. We aimed to evaluate tuberculosis outcomes before and during the pandemic in general and in unhoused populations in São Paulo, Brazil.
METHODS: We performed a retrospective cohort study that compared tuberculosis outcomes between the unhoused and general populations using data from 2017 to 2019 and 2020 to 2022. Unfavorable outcomes were defined as loss to follow-up, treatment failure, death, toxicity, and resistance to drugs. Cox regression models and Kaplan–Meier curves were used to evaluate the data.
RESULTS: Among 47,293 patients diagnosed with tuberculosis using the National Notifiable Diseases Information System (SINAN) between January 1, 2017, and December 31, 2021, 29,247 patients were included in our study. Patients diagnosed with TB during the pandemic were more likely to have unfavorable outcomes in the general population (hazard ratio [HR], 1.45, [95% confidence interval (CI), 1.37 to 1.55], $p < 0.001$), but not in the unhoused population. Patients with lost to follow-up (HR, 1.42, 95% CI 1.21-1.66, $p < 0.001$) or hospitalized (HR, 1.50, 95%CI 1.29-1.74, $p < 0.001$) were more likely to experience unfavorable outcomes in the unhoused population.
CONCLUSIONS: In conclusion, during the pandemic of COVID-19 period the tuberculosis care was not affected in the specific unhoused population but rather affected the general population in the largest city of São Paulo, Brazil.

DOI: 10.1186/s12889-025-23491-9
PMCID: PMC12219442
PMID: 40604738 [Indexed for MEDLINE]

Conflict of interest statement: Declarations. Ethics approval and consent to participate: Not applicable. Competing interests: The authors declare no competing interests.

86. Genotyping and transmission analysis of Mycobacterium tuberculosis in a pediatric population in Czech Republic and Slovakia.

BMC Infect Dis. 2025 Jul 3;25(1):891. doi: 10.1186/s12879-025-11284-9.

Mäsiarová S(1), Dvořáková V(2), Hromádková M(2), Norman A(3), Kunč P(4)(5), Fábry J(4)(5), Hnilicová J(6), Porvazník I(7)(8), Solovič I(7)(8), Rasmussen EM(3), Mokrý J(1), Doležalová K(#)(9), Dohál M(#)(10).

Author information:
(1)Department of Pharmacology, Jessenius Faculty of Medicine in Martin, Comenius University, Bratislava, Slovakia.
(2)National Institute of Public Health, Prague, Czech Republic.
(3)International Reference Laboratory of Mycobacteriology, Statens Serum Institut, Copenhagen, Denmark.
(4)Clinic of Pediatric Respiratory Diseases and Tuberculosis, National Institute of Pediatric Tuberculosis and Respiratory Diseases, Dolny Smokovec, Jessenius Faculty of Medicine in Martin, Comenius University, Bratislava, Slovakia.
(5)Department of Pathological Physiology, Jessenius Faculty of Medicine in Martin, Comenius University, Bratislava, Slovakia.
(6)Department of Genetics and Microbiology, Faculty of Science, Charles University, Prague, Czech Republic.
(7)National Institute of Tuberculosis Lung Diseases and Thoracic Surgery, Vyšné Hágy, Slovakia.
(8)Faculty of Health, Catholic University, Ružomberok, Slovakia.
(9)Department of Paediatrics of the First Faculty of Medicine, Charles University, Thomayer University Hospital, Prague, Czech Republic.
(10)Biomedical Centre Martin, Jessenius Faculty of Medicine in Martin, Comenius University, Bratislava, Slovakia. matus.dohal@uniba.sk.
(#)Contributed equally

BACKGROUND: Tuberculosis remains a global health concern, with rising pediatric

and adolescent cases. The advancement of diagnostic strategies is crucial for effective control, with whole-genome sequencing emerging as a promising tool. This study explores using whole-genome sequencing in pediatric Tuberculosis.
METHODS: Mycobacterium tuberculosis isolates from pediatric patients and their contacts were collected between January 2023 and June 2024 in Slovakia and the Czech Republic. The isolates were subjected to WGS to characterize the resistance patterns and transmission.
RESULTS: The study included 37 patients in total-30 pediatric cases and 7 adult index cases-with a single M. tuberculosis isolate collected per patient. The phylogenetic analysis results revealed that 32 out of 37 (86.5%) isolates belonged to the Euro-American lineage. Five isolates (13.5%) belonged to the East-Asian lineage. Genotypic resistance to at least one drug was confirmed in 6 patients (16%). 24 patients were divided into 9 clusters (65%), leaving 13 unclustered (35%). Moreover, the concordance between the identification of source case by WGS and epidemiological anamnesis was confirmed in 60% of patients.
CONCLUSIONS: Epidemiological data may not always provide accurate insights into the transmission of TB. Consequently, integrating molecular methods, such as WGS, is essential to enhance the reliability and precision of epidemiological analyses.

DOI: 10.1186/s12879-025-11284-9
PMCID: PMC12225057
PMID: 40610922 [Indexed for MEDLINE]

Conflict of interest statement: Declarations. Ethics approval and consent to participate: The study was conducted following the principles described in the Declaration of Helsinki and was approved and was approved by the Ethical Committee of the Jessenius Faculty of Medicine in Martin, Comenius University Bratislava (EK65/2021). No informed consent was required from patients, as the study involved only bacterial cultures and did not include any clinical material obtained directly from human subjects. The data used in this article was fully anonymized following ethical guidelines and the General Data Protection Regulation (GDPR) to ensure the privacy and confidentiality of all individuals involved. Consent for publication: During the preparation of this work the author(s) used chatgpt in order to enhance the clarity and readability of the text. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication. Competing interests: The authors declare no competing interests.

87. Development and in vitro evaluation of 1,4,7-triazacyclononane-coupled β-lactams

against metallo-β-lactamase producing bacteria.

RSC Adv. 2025 Jul 7;15(29):23427-23440. doi: 10.1039/d5ra01842k. eCollection 2025 Jul 4.

Shungube M(1), Reddy N(1)(2), Ghazi T(3), Govender KB(1), Singh R(3)(4), Kajee A(3)(4), Chuturgoon A(3), Kruger HG(1), Arvidsson PI(1)(5), Tiwari D(1)(6), Govender T(7), Naicker T(1).

Author information:
(1)Catalysis and Peptide Research Unit, University of KwaZulu-Natal Durban 4001 South Africa govenderthav@icloud.com naickert1@ukzn.ac.za +27 312601845.
(2)Office of AIDS and TB, South African Medical Research Council 1 Soutpansberg Road Pretoria South Africa.
(3)School of Laboratory Medicine and Medical Sciences, College of Health Sciences, University of KwaZulu-Natal Durban 4041 South Africa.
(4)Department of Medical Microbiology, KwaZulu-Natal Academic Complex, National Health Laboratory Service Durban South Africa.
(5)Science for Life Laboratory, Drug Discovery & Development Platform & Division of Translational Medicine and Chemical Biology, Department of Medical Biochemistry and Biophysics, Karolinska Institutet Stockholm Sweden.
(6)Hericure HealthCare Pvt Ltd 412, Shree Ganesh Ace Arcade, Business Tower, NR Kokane Chowk Pimple Saudagar Pune-17 India.
(7)Department of Chemistry, University of Zululand Private Bag X1001 KwaDlangezwa 3886 South Africa.

Antimicrobial resistance (AMR) is a critical global issue, particularly against β-lactam antibiotics, which comprise over 60% of prescriptions. Metallo-β-lactamases (MBLs) are especially concerning as they inactivate nearly all β-lactams, except monobactams. Unlike serine-β-lactamases (SBLs), for which inhibitors exist, there are no clinically approved MBL inhibitors; only taniborbactam is in pre-registration. This study introduces eight new MBL inhibitors (13a-f, 14a-b), designed using a 1,4,7-triazacyclononane (NO3PY) chelator linked to a β-lactam. These inhibitors restored the efficacy of meropenem, reducing its minimum inhibitory concentration (MIC) against MBL-expressing pathogens to <2 mg L-1. Time-kill assays confirmed bactericidal activity, with this series being non-toxic and highly specific, these compounds hold promising potential as MBL inhibitors.

DOI: 10.1039/d5ra01842k
PMCID: PMC12230942
PMID: 40626067

Conflict of interest statement: The authors report there are no competing interests to declare.

88. Innovo GenMax MTB-RIF/INH: a moderate-complexity automated NAAT for rapid simultaneous detection of Mycobacterium tuberculosis complex and rifampin/isoniazid resistance.

Front Cell Infect Microbiol. 2025 Jun 30;15:1600170. doi: 10.3389/fcimb.2025.1600170. eCollection 2025.

Ou X(#)(1), Zhao B(#)(1), Zheng H(#)(2), Xing R(1), Sun Q(3), Qin Z(4), Zhang L(4), Cui K(1), Song Y(1), Zheng Y(1), Zhou Y(1), Wang S(1), Xia H(1), Zhao Y(1).

Author information:
(1)National Key Laboratory of Intelligent Tracking and Forecasting for Infectious Diseases, National Center for Tuberculosis Control and Prevention, Chinese Center for Disease Control and Prevention, Beijing, China.
(2)Beijing Key Laboratory of Pediatric Respiratory Infection Diseases, Key Laboratory of Major Diseases in Children, Ministry of Education, National Clinical Research Center for Respiratory Diseases, Laboratory of Respiratory Diseases, Beijing Pediatric Research Institute, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing, China.
(3)Microbial Inspection Department, Changping District Center for Disease Control and Prevention, Beijing, China.
(4)Center for Accurate Detection of Tuberculosis, Tianjin Haihe Hospital, Tianjin, China.
(#)Contributed equally

OBJECTIVE: Given the increase of treatment failure, relapse and acquired resistance observed in isoniazid (INH) resistance, there is an urgent to improve rifampin (RIF) -priority based diagnostic strategies. Therefore, we evaluated the performance of Innovo GenMax MTB-RIF/INH (GenMax), a moderate- complexity automated nucleic acid amplification test (NAAT), for detecting Mycobacterium tuberculosis complex (MTBC) and resistance to RIF and INH.
METHODS: Analytical sensitivity (limit of detection, LOD) was determined using serial dilutions of Mycobacterium tuberculosis H37Rv (ATCC 27249) strains. Diagnostic accuracy was assessed in clinical sputum specimens against microbiological reference standards (MRS: positive by smear microscopy, culture or Xpert MTB/RIF for diagnosis of TB) and phenotypic drug susceptibility testing (DST). Discordant results were resolved by sequencing resistance genes (IS6110,

rpoB, katG, inhA, ahpC) and follow-up diagnosis results.
RESULTS: GenMax demonstrated a calculated LOD of 8.8 CFU/mL (95% CI: 7.4-11.4) for MTBC, 674.1 CFU/mL (95% CI: 578.8-923.5) for RIF resistance, and 747.3 CFU/mL (95% CI: 613.7-1081.3) for INH resistance. In clinical evaluation, the sensitivity and specificity for MTBC detection were 97.52% (95% CI: 92.38-99.36) and 93.65% (95% CI: 88.91-96.53), respectively. For RIF and INH resistance, sensitivities were 88.46% (95% CI: 68.72-96.97) and 85.19% (95% CI: 65.39-95.14), with specificity of 92.42% (95% CI: 82.50-97.18) and 94.12% (95% CI: 84.86-98.10).
CONCLUSION: Innovo GenMax MTB-RIF/INH is a rapid and automated assay with high sensitivity for MTBC detection, suitable for decentralized settings. While its performance for RIF/INH resistance detection is competitive with existing assays, its sensitivity remains gaps relative to WHO targets. Further optimization, particularly through expanded probe coverage, is needed to bridge this gap and ensure reliable detection in clinical settings.

DOI: 10.3389/fcimb.2025.1600170
PMCID: PMC12256539
PMID: 40661969 [Indexed for MEDLINE]

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

89. Sutezolid in combination with bedaquiline, delamanid, and moxifloxacin for pulmonary tuberculosis (PanACEA-SUDOCU-01): a prospective, open-label, randomised, phase 2b dose-finding trial.

Lancet Infect Dis. 2025 Jul 8:S1473-3099(25)00213-0. doi: 10.1016/S1473-3099(25)00213-0. Online ahead of print.

Heinrich N(1), Manyama C(2), Koele SE(3), Mpagama S(4), Mhimbira F(5), Sebe M(6), Wallis RS(6), Ntinginya N(7), Liyoyo A(4), Huglin B(5), Minja LT(7), Wagnerberger L(8), Stoycheva K(8), Zumba T(5), Noreña I(8), Peter DD(4), Makkan H(6), Sloan DJ(9), Brake LT(3), Schildkraut J(3), Aarnoutse RE(3), McHugh TD(10), Wildner L(10), Boeree M(11), Aldana BH(12), Phillips PPJ(12), Hoelscher M(13), Svensson EM(14); PanACEA consortium.

Collaborators: Hoelscher M, Dreisbach J, Wagnerberger L, Heinrich N, Razid A, Stoycheva K, Dierig A, Jarchow-MacDonald A, Noreña I, Paramo Diaz L, Astudillo

R, Basson E, Behnke AL, Sloan D, Sabiiti W, Gillespie S, Te Brake L, Svensson E, Mouhdad C, Aarnoutse R, Boeree M, Stemkens R, Koele S, van der Feltz I, Bateson A, Hunt R, McHugh TD, Muraro Wildner L, Solanki P, Phillips P, Gong X, Aldana B, Crook A, Dawson R, Narunsky K, Arnolds S, Diacon A, de Jager V, Sanne I, Rassool M, Churchyard G, Sebe M, Makkan H, Mokaba L, Madikizela N, Mdluli J, Sithole J, Wallis R, Beattie T, Ntinginya NE, Mangu C, Manyama C, Sabi I, Mtafya B, Minja LT, Chimbe O, Ngaraguza B, Mhimbira F, Mbeya B, Zumba T, Chibunu N, Sasamalo M, Reither K, Jugheli L, Kibiki G, Semvua H, Mpagama S, Liyoyo A, Adegbite BR, Adegnika AA, Grobusch MP, Kirenga B, Khosa C, Timana I, Nliwasa M, Mukoka M.

Author information:
(1)Institute of Infectious Diseases and Tropical Medicine, LMU University Hospital, LMU Munich, Munich, Germany; German Center for Infection Research, Munich Partner Site, Munich, Germany; Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Immunology, Infection and Pandemic Research, Munich, Germany. Electronic address: norbert.heinrich@med.uni-muenchen.de.
(2)National Institute for Medical Research, Mbeya, Tanzania; Center for International Health CIH, LMU Munich, Munich, Germany.
(3)Department of Pharmacy, Pharmacology and Toxicology, Radboud University Medical Center, Nijmegen, Netherlands.
(4)Kibon'goto Infectious Disease Hospital, Moshi, Tanzania.
(5)Ifakara Health Institute, Bagamoyo Research and Training Unit, Dar es Salaam, Tanzania.
(6)The Aurum Institute, Johannesburg, South Africa.
(7)National Institute for Medical Research, Mbeya, Tanzania.
(8)Institute of Infectious Diseases and Tropical Medicine, LMU University Hospital, LMU Munich, Munich, Germany.
(9)University of St Andrews, St Andrews, UK.
(10)UCL Centre for Clinical Microbiology, University College London, London, UK.
(11)Department of Pulmonary Diseases, Radboud University Medical Center, Nijmegen, Netherlands.
(12)UCSF Center for Tuberculosis, University of California San Francisco, San Francisco, CA, USA.
(13)Institute of Infectious Diseases and Tropical Medicine, LMU University Hospital, LMU Munich, Munich, Germany; German Center for Infection Research, Munich Partner Site, Munich, Germany; Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Immunology, Infection and Pandemic Research, Munich, Germany; Unit Global Health, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany.
(14)Department of Pharmacy, Pharmacology and Toxicology, Radboud University Medical Center, Nijmegen, Netherlands; Department of Pharmacy, Uppsala University, Uppsala, Sweden.

BACKGROUND: Linezolid is a key component globally in first-line therapy for

drug-resistant tuberculosis but has considerable toxicity. New and safer alternative oxazolidinones are needed. Sutezolid is one such promising alternative. We aimed to evaluate preliminary efficacy and safety of sutezolid and to identify an optimal dose.
METHODS: PanACEA-SUDOCU-01 was a prospective, open-label, randomised, phase 2b dose-finding study in four tuberculosis trial sites in Tanzania and South Africa. Adults aged 18-65 years with newly diagnosed, drug-sensitive, smear-positive tuberculosis were enrolled and randomly assigned (1:1:1:1:1) by a probabilistic minimisation algorithm using a web-based interface, stratified by site, sex, and HIV status, to receive no sutezolid (U0), sutezolid 600 mg once daily (U600), sutezolid 1200 mg once daily (U1200), sutezolid 600 mg twice daily (U600BD), or sutezolid 800 mg twice daily (U800BD), all administered orally for 12 weeks followed by standard therapy for 6 months. All participants received oral bedaquiline (400 mg once daily for 14 days followed by 200 mg thrice weekly), oral delamanid (100 mg twice daily), and oral moxifloxacin (400 mg once daily). For the primary endpoint, measured in the modified intention-to-treat population, sputum samples were taken weekly to measure the change in bacterial load measured by time to positivity using the mycobacterial growth indicator tube system. Safety was assessed through weekly electrocardiography, safety blood tests, vision testing, and physical and neurological examinations. Intensive pharmacokinetic measurements were done on day 14 to determine exposure to sutezolid, bedaquiline, delamanid, and moxifloxacin. This trial is registered with ClinicalTrials.gov (NCT03959566).
FINDINGS: Between May 20, 2021, and Feb 17, 2022, 186 individuals were screened for eligibility, 75 of whom were enrolled and randomly assigned to U0 (n=16), U600 (n=15), U1200 (n=14), U600BD (n=15), or U800BD (n=15). 56 (75%) participants were male and 19 (25%) were female. The final pharmacokinetic-pharmacodynamic model showed a benefit of sutezolid, with an increase in time to positivity slope steepness of 16·7% (95% CI 0·7-35·0) at the maximum concentration typical for the 1200 mg dose, compared with no sutezolid exposure. A maximum effect of sutezolid exposure was not observed within the investigated dose range. Six (8%) participants (one in the U600 group, two in the U600BD group, one in the U800BD group, and two retrospectively identified in the U600 group) had an increase in a QT interval using Fridericia correction greater than 60 ms from baseline. Two (3%) participants in the U600BD group had grade 4 adverse events, one each of neutropenia and hepatotoxicity, but they were not deemed associated with the use of sutezolid by the investigators. No neuropathy was reported.
INTERPRETATION: Sutezolid, combined with bedaquiline, delamanid, and moxifloxacin, was shown to be efficacious and added activity to the background drug combination, although we cannot make a final dose recommendation yet. This study provides valuable information for the selection of sutezolid doses for future studies, and described no oxazolidinone class toxicities at the doses used.

FUNDING: EDCTP2 programme funded by the EU; German Ministry for Education and Research; German Center for Infection Research; and Nederlandse Organisatie voor Wetenschappelijk Onderzoek.

DOI: 10.1016/S1473-3099(25)00213-0
PMID: 40645196

Conflict of interest statement: Declaration of interests EMS declares receiving funding to her institution from Janssen Pharmaceuticals for a scientific project related to bedaquiline, and from TB Alliance for projects related to paediatric development of pretomanid. All authors report receiving funding from LigaChem Biosciences to their institutions for the conduct of the DECODE study on delpazolid, a competing drug candidate.

90. Evaluation of the PATHFAST TB LAM Ag assay as a treatment monitoring tool for pulmonary tuberculosis in Nairobi, Kenya.

Trop Med Health. 2025 Jul 1;53(1):89. doi: 10.1186/s41182-025-00771-z.

Orina F(#)(1), Hikone M(#)(2), Saito N(3), Ong'ang'o J(1), Nyerere A(4), Songoro E(4), Meme H(1).

Author information:
(1)Center for Respiratory Disease Research, Kenya Medical Research Institute, Nairobi, Kenya.
(2)Kenya Research Station, Institute of Tropical Medicine, Nagasaki University, Nagasaki, Japan.
(3)Kenya Research Station, Institute of Tropical Medicine, Nagasaki University, Nagasaki, Japan. nsaito@nagasaki-u.ac.jp.
(4)Department of Medical Microbiology, College of Health Sciences, Jomo Kenyatta University of Agriculture and Technology, Nairobi, Kenya.
(#)Contributed equally

BACKGROUND: Treatment monitoring is important in pulmonary tuberculosis (PTB) management, since prolonged treatment necessitates regular assessments to prevent treatment failure and the emergence of drug-resistant strains. However, the lack of a simple, rapid, and reliable treatment monitoring tool (TMT) remains a major challenge. We evaluated the utility of measuring sputum lipoarabinomannan (LAM) concentration by the PATHFAST TB LAM Ag assay (PHC

Corporation, Tokyo, Japan) as a TMT in patients with PTB in Nairobi, Kenya.
METHODS: We retrospectively analyzed sputum LAM levels via the PATHFAST TB LAM Ag assay from a Nairobi cohort of patients with PTB and compared these results with conventional microbiological tests (acid-fast bacilli [AFB] smear microscopy; mycobacterial growth indicator tube [MGIT] culture). Stored sputum pellets processed with N-acetyl-L-cysteine (NALC)-NaOH were used for LAM measurement. Serial LAM concentrations measured every 2 weeks over an 8-week period were compared across bacterial load categories to assess correlations with AFB smear grades and culture results using the Kruskal-Wallis and Mann-Whitney U tests.
RESULTS: The 98 patients included here had a median age of 37 years (Interquartile Range: 27-44). The majority were men (74/98, 75.5%) and the MGIT culture was positive for 89 (90.8%) of them. Patients with elevated baseline LAM concentrations showed a significant reduction in LAM levels with treatment (90% median reduction by week 8), whereas those with low baseline LAM concentrations did not show a declining trend. Sputum LAM levels were significantly higher in culture-positive samples compared to culture-negative samples (23.8 pg/mL vs. 10.8 pg/mL, $P < 0.001$). Sputum LAM levels showed a significant correlation with AFB smear grades, with median concentrations increasing progressively from 11.3 pg/mL in smear-negative samples to 19.7 pg/mL in scanty/1 + samples, and 46.7 pg/mL in 2 + /3 + samples ($P = 0.0001$). LAM levels were significantly higher in culture-positive/AFB-positive sputum samples (viable bacilli) than in culture-negative/AFB-positive samples (non-viable bacilli) ($P < 0.0001$).
CONCLUSION: Our findings revealed that sputum LAM concentration declined during TB treatment, particularly among patients with high baseline levels, and correlated with AFB smear grades and culture results. Additionally, LAM concentrations differed between culture-positive and culture-negative samples among AFB smear-positive samples. Further prospective studies are needed to assess LAM levels as a TMT.

DOI: 10.1186/s41182-025-00771-z
PMCID: PMC12210661
PMID: 40598435

Conflict of interest statement: Declarations. Ethics approval and consent to participate: The study protocol, including the follow-up and assessment of LAM levels using the PATHFAST TB LAM Ag assay, was reviewed and approved by the KEMRI-SERU (Ethical Approval Number: SERU 4595). All participants provided written informed consent prior to enrollment, including consent for serial sputum collection throughout the follow-up period. Consent for publication: Not applicable. Competing interests: The authors declare no competing interests.

91. Elimination of senescent cells with senolytic host-directed therapy reduces tuberculosis progression in mice.

bioRxiv [Preprint]. 2025 Jul 3:2025.03.28.645957. doi: 10.1101/2025.03.28.645957.

Shee S, Martinez-Martinez YB, Koleske B, Yabaji S, Kobzik L, Kramnik I, Bishai W.

By eliciting lung necrosis, which enhances aerosol transmission, Mycobacterium tuberculosis (Mtb) sustains its long-term survival as a human pathogen. In studying the human-like necrotic granuloma lesions characteristic of Mtb -infected B6.Sst1S mice, we found that lung myeloid cells display elevated senescence markers: cell cycle arrest proteins p21 and p16, the DNA damage marker γH2A.X, senescence-associated β-galactosidase activity, and senescence-associated secretory phenotype (SASP). These markers were also elevated in Mtb -infected aged wild type (WT) mice but not in young WT mice. Global transcriptomics data revealed upregulation of pro-survival (PI3K, MAPK) and anti-apoptotic pathways in Mtb -infected B6.Sst1S macrophages. As senescent cells are terminally growth-arrested yet metabolically active cells that release tissue-damaging, immunosuppressive SASP, we treated Mtb -infected mice with a cocktail of three senolytic drugs (dasatinib, quercetin, and fisetin) designed to kill senescent cells. Senolytic drug treatment prolonged survival and reduced Mtb lung counts in B6.Sst1S and aged WT mice to a greater degree than young WT mice and concomitantly reduced lung senescence markers. These findings indicate that (1) Mtb infection may induce lung myeloid cells to enter a senescent state and that these cells may promote disease progression, and (2) senolytic drugs merit consideration for human clinical trials against tuberculosis (TB).
HIGHLIGHTS: Mtb lung infection results in recruitment of both restrictive and permissive myeloid cells to the nascent granuloma. Mtb infection induces certain permissive myeloid cells to enter a senescent state, characterized by cell cycle arrest and they promote local immunosuppression. Treatment with a Senolytic drug cocktail, which kills senescent cells, augments host resistance against Mtb proliferation, lethality and immunopathology.

DOI: 10.1101/2025.03.28.645957
PMCID: PMC12236815
PMID: 40631209

92. Drug resistance of Mycobacterium tuberculosis to linezolid and delamanid: a case report from Bukavu, Democratic Republic of Congo.

BMC Infect Dis. 2025 Jul 12;25(1):913. doi: 10.1186/s12879-025-11348-w.

Bisimwa BC(1)(2), Bahizire E(3)(4), Kiselinova M(5), Byela V(3), Ngabonziza JCS(6)(7), Hakizayezu F(8), Runyambo D(8), Meehan CJ(9)(10), Mulders W(9), Cuella-Martin I(9), Rigouts L(9)(11), Birembano F(12), Callens S(5), de Jong BC(9), Kaswa M(12).

Author information:
(1)Center for Tropical Diseases & Global Health, Université Catholique de Bukavu, Bukavu, South Kivu, Congo. bcasinga@gmail.com.
(2)Faculty of Medicine and Health Sciences, Ghent University, Ghent, Belgium. bcasinga@gmail.com.
(3)Center for Tropical Diseases & Global Health, Université Catholique de Bukavu, Bukavu, South Kivu, Congo.
(4)Department of Medical Microbiology, University of Nairobi, Nairobi, Kenya.
(5)Department of Internal Medicine, Ghent University Hospital, Ghent, Belgium.
(6)Research Innovation and Data Science Division, Rwanda Biomedical Centre, Kigali, Rwanda.
(7)Department of Clinical Biology, University of Rwanda, Kigali, Rwanda.
(8)Rwanda Biomedical Centre, National Laboratory Division, Kigali, Rwanda.
(9)Mycobacteriology Unit, Department of Biomedical Sciences, Institute of Tropical Medicine, Antwerp, Belgium.
(10)Department of Biosciences, Nottingham Trent University, Nottingham, UK.
(11)Biomedical Sciences, Antwerp University, Antwerp, Belgium.
(12)National Tuberculosis Program, Kinshasa, Kinshasa, Congo.

The emergence of resistance is of great concern in the control of TB, especially to the new and repurposed drugs needed for the treatment of rifampicin resistance. We report a patient from South Kivu in the Eastern Democratic Republic of the Congo with primary resistance to delamanid and linezolid without treatment experience with these drugs. The identification of novel resistance mutations raises concerns about the potential global spread and poor outcomes of the WHO-recommended oral treatment regimens, highlighting the need for the urgent rollout of DST.

DOI: 10.1186/s12879-025-11348-w
PMCID: PMC12255050
PMID: 40652177 [Indexed for MEDLINE]

Conflict of interest statement: Declarations. Ethics approval and consent to participate: Ethics approval was received from the Institutional Ethics Committee of the Université Catholique de Bukavu (reference number

UCB/CIES/NC/015/2022). The patient voluntarily agreed to participate in the study. Consent for publication: The patient gave written informed consent for the publication of the data. Competing interests: The authors declare no competing interests.

93. Structure-based design, synthesis, computational screening and biological evaluation of novel pyrrole fused pyrimidine derivatives targeting InhA enzyme.

RSC Adv. 2025 Jul 21;15(32):25776-25798. doi: 10.1039/d5ra03004h. eCollection 2025 Jul 21.

Singh D(1), Parkali PM(1), Hani U(2), Osmani RAM(3), Haider N(4), Kumari J(5), Sriram D(5), Lherbet C(6), Revan Siddappa BC(7), Dixit SR(1).

Author information:
(1)Department of Pharmaceutical Chemistry, JSS College of Pharmacy, JSS Academy of Higher Education and Research Sri Shivarathreeshwara Nagar Mysuru Karnataka 570015 India sheshagiridixit@jssuni.edu.in +91 721107207.
(2)Department of Pharmaceutics, College of Pharmacy, King Khalid University Guraiger Abha 62529 Saudi Arabia.
(3)Department of Pharmaceutics, College of Pharmacy, King Khalid University Al-Faraa Abha 61421 Saudi Arabia.
(4)Department of Pathology, College of Medicine, King Khalid University Guraiger Abha 62529 Saudi Arabia.
(5)Department of Pharmacy, Birla Institute of Technology and Science-Pilani, Hyderabad Campus Jawahar Nagar Hyderabad Telangana 500 078 India.
(6)Université de Toulouse, CNRS, Laboratoire de Synthèse et Physico-Chimie de Molécules d'Intérêt Biologique (LSCPMIB) 118 Route de Narbonne 31062 Toulouse Cedex 09 France.
(7)Department of Pharmaceutical Chemistry, NGSM Institute of Pharmaceutical Sciences (NGSMIPS), Nitte (Deemed to be University) Mangalore Karnataka 575018 India.

In this study, a series of 12 novel pyrrolyl chalcones and 22 pyrrole-fused pyrimidine derivatives were synthesized with good yields. Structural characterization was performed using FT-IR, NMR, and mass spectrometry techniques. The antitubercular potential of these compounds was evaluated using the microplate alamar blue assay (MABA). Among the synthesized compounds, compound 4g exhibited the highest potency, with a minimum inhibitory concentration (MIC) of 0.78 mg mL-1 demonstrating greater efficacy than the standard drug isoniazid. Several other analogues also showed moderate to good inhibitory activity. Selected compounds were further assessed for cytotoxicity using human lung cancer (A549) and normal RAW cell lines, revealing low toxicity

profiles. Enzymatic assays indicated that compound 4g achieved 36% inhibition of InhA at a concentration of 50 μM. Additionally, molecular dynamics simulations were conducted to analyze the stability of the protein-ligand complexes, suggesting that these compounds hold potential for future development as InhA inhibitors in the fight against MDR-TB.

DOI: 10.1039/d5ra03004h
PMCID: PMC12278818
PMID: 40697459

Conflict of interest statement: The authors declare no financial conflicts of interest or personal affiliations that could have influenced the research conducted in this study or any kind of conflict of interest. The authors declare the following financial interests/personal relationships which may be considered as potential competing interests. An Indian patent entitled “Synthetic strategies: methods for producing pyrimidine as anti-tubercular agent” has been granted related to this work (Indian Patent No. 568101 granted on 30th June-2025).

94. Delpazolid in combination with bedaquiline, delamanid, and moxifloxacin for pulmonary tuberculosis (PanACEA-DECODE-01): a prospective, randomised, open-label, phase 2b, dose-finding trial.

Lancet Infect Dis. 2025 Jul 8:S1473-3099(25)00289-0. doi: 10.1016/S1473-3099(25)00289-0. Online ahead of print.

Minja LT(1), van der Feltz I(2), Manyama C(3), Mpagama S(4), Mhimbira F(5), Noreña I(6), Sebe M(7), Rassool M(8), Wallis RS(7), Ntinginya N(1), Liyoyo A(4), Mbeya B(5), Wagnerberger L(6), Zumba T(5), Peter DD(4), Makkan H(7), Sloan DJ(9), Brake LT(2), Schildkraut JA(2), Aarnoutse R(2), McHugh TD(10), Wildner L(10), Boeree MJ(11), Geiter L(12), Cho YL(12), Aldana BH(13), Phillips PPJ(13), Hoelscher M(14), Svensson EM(15), Heinrich N(16); PanACEA consortium.

Collaborators: Hoelscher M, Dreisbach J, Wagnerberger L, Heinrich N, Razid A, Stoycheva K, Dierig A, Jarchow-MacDonald A, Noreña I, Paramo Diaz L, Astudillo R, Basson E, Behnke AL, Sloan D, Sabiiti W, Gillespie S, Te Brake L, Svensson E, Mouhdad C, Aarnoutse R, Boeree M, Stemkens R, Koele S, van der Feltz I, Bateson A, Hunt R, McHugh TD, Muraro Wildner L, Solanki P, Phillips P, Gong X, Aldana B, Crook A, Dawson R, Narunsky K, Arnolds S, Diacon A, de Jager V, Sanne I, Rassool M, Churchyard G, Sebe M, Makkan H, Mokaba L, Madikizela N, Mdluli J, Sithole J, Wallis R, Beattie T, Ntinginya NE, Mangu C, Manyama C, Sabi I, Mtafya B, Minja

LT, Chimbe O, Ngaraguza B, Mhimbira F, Mbeya B, Zumba T, Chibunu N, Sasamalo M, Reither K, Jugheli L, Kibiki G, Semvua H, Mpagama S, Liyoyo A, Adegbite BR, Adegnika AA, Grobusch MP, Kirenga B, Khosa C, Timana I, Nliwasa M, Mukoka M.

Author information:
(1)National Institute for Medical Research, Mbeya, Tanzania.
(2)Department of Pharmacy, Pharmacology and, Toxicology, Radboud University Medical Center, Nijmegen, Netherlands.
(3)National Institute for Medical Research, Mbeya, Tanzania; Center for International Health CIH, LMU Munich, Munich, Germany.
(4)Kibon'goto Infectious Disease Hospital, Moshi, Tanzania.
(5)Ifakara Health Institute, Bagamoyo Research and Training Unit, Dar es Salaam, Tanzania.
(6)Institute of Infectious Diseases and Tropical Medicine, LMU University Hospital, LMU Munich, Munich, Germany; German Center for Infection Research, Munich Partner Site, Munich, Germany.
(7)The Aurum Institute, Johannesburg, South Africa.
(8)Clinical HIV Research Unit, Wits Health Consortium, Health Science Research Office, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa.
(9)Department of Pharmacy, Pharmacology and, Toxicology, Radboud University Medical Center, Nijmegen, Netherlands; University of St Andrews, St Andrews, UK.
(10)UCL Centre for Clinical Microbiology, University College London, London, UK.
(11)Department of Pulmonary Diseases, Radboud University Medical Center, Nijmegen, Netherlands.
(12)LigaChem Biosciences, Daejeon, South Korea.
(13)University of California San Francisco Center for Tuberculosis, University of California San Francisco, San Francisco, CA, USA.
(14)Institute of Infectious Diseases and Tropical Medicine, LMU University Hospital, LMU Munich, Munich, Germany; German Center for Infection Research, Munich Partner Site, Munich, Germany; Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Immunology, Infection, and Pandemic Research, Munich, Germany; Unit Global Health, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany.
(15)Department of Pharmacy, Pharmacology and, Toxicology, Radboud University Medical Center, Nijmegen, Netherlands; Department of Pharmacy, Uppsala University, Uppsala, Sweden.
(16)Institute of Infectious Diseases and Tropical Medicine, LMU University Hospital, LMU Munich, Munich, Germany; German Center for Infection Research, Munich Partner Site, Munich, Germany; Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Immunology, Infection, and Pandemic Research, Munich, Germany. Electronic address: norbert.heinrich@med.uni-muenchen.de.

BACKGROUND: Linezolid plays a crucial role in the first-line treatment of

drug-resistant tuberculosis globally. Its prolonged use can lead to neurological and haematological toxicity, highlighting the need for safer oxazolidinones. Delpazolid, a novel oxazolidinone, might be safer. We aimed to evaluate the safety and efficacy of delpazolid and identify an optimal dose.
METHODS: PanACEA-DECODE-01 was a prospective, randomised, open-label, phase 2b, multicentre, dose-finding trial done in five tuberculosis trial sites in Tanzania and South Africa. Adults aged 18-65 years, who weighed 40-90 kg, and had newly diagnosed, smear positive pulmonary tuberculosis were randomly assigned (1:1:1:1:1) through centralised allocation, using a probabilistic minimisation algorithm to receive no delpazolid (D0), delpazolid 400 mg once daily (D400), delpazolid 800 mg once daily (D800), delpazolid 1200 mg once daily (D1200), or delpazolid 800 mg twice daily (D800BD), all administered orally for 16 weeks with follow-up to week 52. All participants received bedaquiline (400 mg orally once daily for the first 14 days, then 200 mg orally thrice weekly), delamanid (100 mg orally twice daily), and moxifloxacin (400 mg orally once daily). Randomisation was stratified based on bacterial load in sputum as measured by GeneXpert cycle threshold (<16 vs ≥16), site, and HIV status. The primary efficacy objective was to establish an exposure-response model with the primary endpoint, measured in the modified intention-to-treat population, of change in mycobacterial load measured by time to positivity using the liquid culture mycobacterial growth indicator tube system. A secondary outcome was the time on treatment to sustained conversion to negative sputum culture in liquid media. The primary safety outcome was the occurrence of oxazolidinone class toxicities defined as peripheral or optical neuropathy, incident leukopenia, anaemia or thrombocytopenia, or adverse events in line with tyramine pressor response, all of grade 2 or higher, possibly, probably or definitely related to delpazolid. This study was registered with ClinicalTrials.gov, NCT04550832.
FINDINGS: Between Oct 28, 2021, and Aug 31, 2022, 156 individuals were screened for eligibility, 76 of whom were enrolled and randomly assigned to D0 (n=15), D400 (n=15), D800 (n=15), D1200 (n=16), or D800BD (n=15). 60 (79%) of 76 participants were male and 16 (21%) were female. Population pharmacokinetic-pharmacodynamic modelling suggests maximal microbiological activity at a daily total exposure of delpazolid (area under the concentration curve from 0 h to 24 h [AUC0-24]) of 50 mg/L per h; close to the median exposure observed after a 1200 mg dose. This maximal effect was estimated at a 38% (95% CI 4-83; p=0·025) faster decline in bacterial load compared with no delpazolid. In the secondary time-to-event analysis, there was no significant difference in time to culture conversion between treatment arms or exposure tertile. When all delpazolid-containing groups were combined, the hazard ratio for the time to sustained culture conversion to negative, comparing all delpazolid-containing groups with the group without delpazolid was 1·53 (95% CI 0·84-2·76). Two drug-related serious adverse events (one gastritis and one anaemia) occurred in the D800BD group, with high individual AUC0-24. Apart from the anaemia and one event of brief, moderate neutropenia observed at only one visit in the D800

group not in line with the characteristics of oxazolidinone class toxicity, no oxazolidinone class toxicities occurred.
INTERPRETATION: The pharmacokinetic-pharmacodynamic modelling results suggest that delpazolid adds efficacy on top of bedaquiline, delamanid, and moxifloxacin; and that a dose of 1200 mg once daily would result in exposures with maximum efficacy. That dose was shown to be safe, raising hope that linezolid toxicities could be averted in long-term treatment. Delpazolid is a promising drug for future tuberculosis treatment regimens and could be widely usable if safety and efficacy are confirmed in larger trials.
FUNDING: LigaChem Biosciences, EDCTP2 programme supported by the EU; German Ministry for Education and Research; German Center for Infection Research; Swiss State Secretariat for Education, Research and Innovation; and Nederlandse Organisatie voor Wetenschappelijk Onderzoek.

DOI: 10.1016/S1473-3099(25)00289-0
PMID: 40645198

Conflict of interest statement: Declaration of interests The following authors received funding to their institutions from LigaChem Biosciences for the PanACEA-DECODE-01 study and European and Developing Countries Clinical Trials Partnership (EDCTP) funding for PanACEA: NN, AL, BHA, BM, FM, HM, IN, IvdF, JAS, LWa, LWi, LtB, MJB, LTM, MR, MS, PPJP, DDP, RA, RSW, SM, TZ, CM, LWi, EMS, NH, and MH. Y-LC and LG received funding from LigaChem Biosciences for the PanACEA-DECODE-01 study. Y-LC is the Senior Vice President and LG is a consultant for LigaChem Biosciences. NH and MH received funding from German Ministry for Education and Research and German Center for Infection Research to their institution. EMS declares receiving funding to her institution from Janssen Pharmaceuticals for a scientific project related to bedaquiline, TB Alliance for projects related to paediatric development of pretomanid, and from EDCTP, Swedish Heart and Lung Foundation, National Institutes of Health, and Unitaid. TDM declares receiving grants or contracts to University College London from EDCTP for PanACEA, for PRACTECAL from Médecins sans Frontières, for SimpliciTB from EDCTP and TB Clinical Trials Collaboration (Global Alliance Against Tuberculosis), and for UNITE4TB from the EU Innovative Medicines Initiative. TDM also participated in the data safety monitoring board for the PORT trial (no payment), was the Chair of Acid Fast Club (UK; unpaid), participated in the expert panel for Africa Research Excellence Fund (unpaid), and is currently the Editor in Chief for the Annals of Clinical Microbiology & Antimicrobials (personal payment). DJS received EDCTP funding for PanACEA to his institution.

95. Light-Induced Synthesis and Radiotheranostic Treatment of Gastric Cancer with (161)Tb-Labeled Monoclonal Antibodies.

JACS Au. 2025 May 22;5(6):2606-2618. doi: 10.1021/jacsau.5c00219. eCollection 2025 Jun 23.

Cieslik PA(1), Roth D(1), Nisli E(1), Genz J(1), Berton C(1), Grundler PV(2), Hillhouse CC(2), Moiseeva AN(2), Nolff M(3), Braband H(1), van der Meulen NP(2), Holland JP(1).

Author information:
(1)Department of Chemistry, University of Zurich, Winterthurerstrasse 190, CH-8057 Zurich, Switzerland.
(2)Paul Scherrer Institute PSI, Forschungsstrasse 111, CH-5232 Villigen, Switzerland.
(3)Klinik für Kleintierchirurgie, Vetsuisse-Fakultät, University of Zurich, Winterthurerstrasse 260, CH-8057 Zurich, Switzerland.

Radiolabeled monoclonal antibodies (mAbs) form a major branch of nuclear medicine and are used in the development of tracers for both diagnostic imaging and molecularly targeted radio-(immuno)-therapy (RIT). Since treatment options for many types of late-stage cancers are limited and these diseases become refractory to classic chemotherapy, new tools are required to improve patient outcomes. The high tumor uptake and specificity of mAbs, coupled with increased therapeutic range of energetic β--emitting radionuclides, offers a potential solution to overcome traditional problems associated with poor tissue penetration of antibody-drug conjugates, chemotherapeutic resistance, and off-target accumulation, which can lead to adverse responses. The challenge is to develop efficient and reliable chemical methods that provide simultaneous selectivity and high stabilization of the radiometal via complexation chemistry, with rapid access to new bioconjugate bonds on protein that avoid the loss of bioactivity. Here, we designed a new octadentate bispidine-chelating system, functionalized with a light-responsive tetrazole unit, and demonstrated the chemoselective derivatization of sulfhydryl groups introduced on the protein surface. High radiolabeling and bioconjugation yields of 161Tb-onartuzumaban engineered mAb fragment targeting the human hepatocyte growth-factor receptor (c-MET; a characteristic biomarker found in clinical samples of several diseases, including gastric adenocarcinomas)were obtained under ambient conditions after 5 min of light-induced coupling. Comprehensive biochemical and animal experiments including cellular binding assays, noninvasive γ-ray imaging, biodistribution studies, and pharmacokinetic measurements established the viability of using 161Tb-onartuzumab to target c-MET expression in vivo.

Subsequent RIT studies in MKN-45 xenograft models demonstrated that the 161Tb-onartuzumab radiotracer formed by photoradiosynthesis permitted low-dose therapy studies that led to efficient targeting and treatment of tumor models. Collectively, the new complexation and chemoselective photoconjugation chemistries overcome some of the limitations in traditional labeling approaches. Photoradiosynthesis represents an excellent platform for building future antibody-based radiotracers for applications in diagnostic and therapeutic medicine.

DOI: 10.1021/jacsau.5c00219
PMCID: PMC12188480
PMID: 40575318

96. Effects of conditional cash transfers and pre-test and post-test tuberculosis counselling on patient outcomes and loss to follow-up across the continuum of care in South Africa: a randomised controlled trial.

Lancet Infect Dis. 2025 Jul;25(7):764-774. doi: 10.1016/S1473-3099(24)00816-8. Epub 2025 Feb 6.

Ismail N(1), Moultrie H(2), Mwansa-Kambafwile J(3), Copas A(4), Izu A(5), Moyo S(6), Skinner D(7), Ismail F(2), Gosce L(8), Omar SV(9), Abubakar I(4), Madhi SA(5).

Author information:
(1)Department of Clinical Microbiology and Infectious Diseases, School of Pathology, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa; National Health Laboratory Service, Johannesburg, South Africa. Electronic address: nazir.ismail@wits.ac.za.
(2)Centre for Tuberculosis, National Institute for Communicable Diseases, a division of the National Health Laboratory Service, Johannesburg, South Africa.
(3)Centre for Tuberculosis, National Institute for Communicable Diseases, a division of the National Health Laboratory Service, Johannesburg, South Africa; School of Public Health and Family Medicine, University of Cape Town, Cape Town, South Africa.
(4)Institute for Global Health, Faculty of Population Health Sciences, School of Life and Medical Sciences, University College London, London, UK.
(5)Department of Clinical Microbiology and Infectious Diseases, School of Pathology, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa; South African Medical Research Council Vaccines and Infectious Diseases Analytics Research Unit, Faculty of Health Sciences,

University of the Witwatersrand, Johannesburg, South Africa.
(6)Human Sciences Research Council, Cape Town, South Africa; Faculty of Medical and Health Sciences, Stellenbosch University, Cape Town, South Africa.
(7)Faculty of Medical and Health Sciences, Stellenbosch University, Cape Town, South Africa.
(8)Institute for Global Health, Faculty of Population Health Sciences, School of Life and Medical Sciences, University College London, London, UK; TB Modelling Group, TB Centre, Department of Infectious Disease Epidemiology, London School of Hygiene & Tropical Medicine, London, UK.
(9)Department of Clinical Microbiology and Infectious Diseases, School of Pathology, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa; Centre for Tuberculosis, National Institute for Communicable Diseases, a division of the National Health Laboratory Service, Johannesburg, South Africa.

BACKGROUND: Economic and behavioural factors lead to poor outcomes in patients with tuberculosis. We investigated the effects of a package of interventions consisting of pre-test and post-test tuberculosis counselling with conditional cash transfers on patient outcomes in adults undergoing investigation for pulmonary tuberculosis.
METHODS: This pragmatic, open-label, individual randomised controlled trial was done in nine clinics in Johannesburg, South Africa. Participants (aged ≥18 years) undergoing investigation for tuberculosis were randomly assigned (1:1) to the intervention group or control group (standard of care) via permuted block randomisation, stratified by clinic; group assignment was concealed using opaque envelopes. The intervention group received pre-test and post-test tuberculosis counselling, and for participants diagnosed with rifampicin-susceptible tuberculosis, a digital payment (R150; approximately US$10) at treatment initiation and each monthly treatment visit. Payments were contingent on timely attendance: 14 days from initial sputum sample collection and within 7 days on either side of their scheduled monthly appointment. The primary endpoint was successful patient outcome (patients who were cured or completed treatment) or unsuccessful patient outcome (pretreatment loss-to-follow-up, on-treatment loss-to-follow-up, development of rifampicin-resistant tuberculosis while on treatment, treatment failure [ie, smear or culture positive at 5 months or later after commencing treatment], or death). The primary outcome was analysed in the modified intention-to-treat population, defined as all randomly assigned participants with rifampicin-susceptible tuberculosis confirmed before the commencement of tuberculosis treatment. Weighted outcome prevalence, relative risks (RRs), and risk differences were calculated using a multivariable Poisson model with robust standard errors. This trial is registered with the Pan African Clinical Trials Registry (PACTR202410708311054) and is completed.
FINDINGS: Between Oct 25, 2018, and Dec 9, 2019, 4110 participants were enrolled and randomly assigned, 2059 to the intervention group and 2051 to the control

group. 381 (9·3%) participants had microbiologically confirmed rifampicin-susceptible pulmonary tuberculosis (195 [9·5%] of 2059 in the intervention group vs 186 [9·1%] of 2051 in the control group; median age 37 years [IQR 30 to 45], 257 [67·5%] male, 124 [32·5%] female). At study closure, primary outcome data were available for 128 (65·6%) of 195 participants in the intervention group and 139 (74·7%) of 186 participants in the control group. 105 (82·0%) of 128 participants in the intervention group and 93 (66·9%) of 139 participants in the control group had a successful patient outcome; 23 (18·0%) of 128 participants in the intervention group and 46 (33·1%) of 139 participants in the control group had an unsuccessful patient outcome. The weighted regression analysis showed a substantial reduction in the risk of unsuccessful patient outcomes in the intervention group compared with the control group (weighted prevalence 15·9% vs 28·6%; RR in weighted population 0·52, 95% CI 0·33 to 0·82; risk difference in weighted population -14·1 percentage points, 95% CI -23·3 to -4·8). Pretreatment loss to follow-up was lower in the intervention group than in the control group (unweighted population: five [3·9%] of 128 participants vs 22 [15·8%] of 139 participants; risk difference in weighted population -9·6 percentage points, 95% CI -14·9 to -4·2).
INTERPRETATION: The package of interventions consisting of pre-test and post-test tuberculosis counselling with conditional cash transfers significantly reduced the risk of unsuccessful tuberculosis patient outcomes, bringing one of the 90-90-90 targets within reach (ie, achieving 90% tuberculosis treatment success). Furthermore, reduction in pretreatment loss to follow-up is expected to reduce transmission and lower incidence of the disease over time.
FUNDING: South African Medical Research Council, UK Medical Research Council, and Newton Fund.

DOI: 10.1016/S1473-3099(24)00816-8
PMCID: PMC12176662
PMID: 39923785 [Indexed for MEDLINE]

Conflict of interest statement: Declaration of interests SAM reports grants to their institution from the Bill & Melinda Gates Foundation, GSK, Pfizer, and MinervaX; clinical trial funding to their institution from Merck, Providence, and Gritstone; honoraria for lectures from GSK; and participation on data safety monitoring boards for PATH, CAPRISA, and Bavarian Nordic. All other authors declare no competing interests.

97. Evaluation of antiretroviral regimen switching options in adults with HIV with sustained viral load non-suppression on dolutegravir, lamivudine, and tenofovir

in eastern, central, southern, and western Africa: a modelling study.

Lancet HIV. 2025 Jun 24:S2352-3018(25)00068-2. doi: 10.1016/S2352-3018(25)00068-2. Online ahead of print.

Phillips AN(1), Bansi-Matharu L(2), van Oosterhout JJ(3), Hyle E(4), van de Vijver D(5), Kouyos R(6), Hong SY(7), Chun H(7), Raizes E(7), Kantor R(8), Jordan MR(9), Vitoria M(10), Ford N(11), Mugurungi O(12), Apollo T(12), Chimberengwa P(13), Meintjes G(14), Siedner M(4), Lundgren J(15), Schapiro J(16), Flexner C(17), Loosli T(6), Cambiano V(2), Smith J(2), Xia R(2), McCluskey S(4), Mewoabi S(18), Calmy A(19), Eholie SP(20), Revill P(21).

Author information:
(1)Institute for Global Health, UCL, London, UK. Electronic address: andrew.phillips@ucl.ac.uk.
(2)Institute for Global Health, UCL, London, UK.
(3)Partners in Hope, Lilongwe, Malawi; David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA, USA.
(4)Massachusetts General Hospital, Boston, MA, USA; Harvard Medical School, Boston, MA, USA.
(5)Erasmus Medical Centre, Erasmus University, Rotterdam, Netherlands.
(6)Department of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich, Zurich, Switzerland; Institute of Medical Virology, University of Zurich, Zurich, Switzerland.
(7)Division of Global HIV and TB, Global Health Center, Centers for Disease Control and Prevention, Atlanta, GA, USA.
(8)Department of Medicine, Brown University Warren Alpert Medical School, Providence, RI, USA.
(9)Department of Medicine and Department of Public Health and Community Medicine, Tufts University School of Medicine, Boston, MA, USA; Global Health and Tropical Medicine, LA-REAL, Instituto de Higiene e Medicina Tropical, Universidade NOVA de Lisboa, Lisbon, Portugal.
(10)Department of Global HIV, Hepatitis, and Sexually Transmitted Infections Programmes, World Health Organization, Geneva, Switzerland.
(11)Department of Global HIV, Hepatitis, and Sexually Transmitted Infections Programmes, World Health Organization, Geneva, Switzerland; Centre for Integrated Data and Epidemiological Research, University of Cape Town, Cape Town, South Africa.
(12)Ministry of Health and Child Care, Harare, Zimbabwe.
(13)Department of Community Medicine, National University of Science and Technology, Bulawayo, Zimbabwe.
(14)Department of Medicine, University of Cape Town, Cape Town, South Africa; Blizard Institute, Queen Mary University of London, London, UK.

(15)Centre of Excellence for Health, Immunity, and Infections, Department of Infectious Diseases, Copenhagen University Hospital-Rigshospitalet, Copenhagen, Denmark; Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark.
(16)National Hemophilia Center, Sheba Medical Center, Ramat Gan, Israel.
(17)Johns Hopkins University School of Medicine, Baltimore, MD, USA.
(18)Department of Microbiology and Parasitology, University of Buea, Buea, Cameroon.
(19)Geneva University Hospitals, Geneva, Switzerland.
(20)Unit of Infectious and Tropical Diseases, Treichville University Teaching Hospital, Abidjan, Côte d'Ivoire.
(21)Centre for Health Economics, University of York, York, UK.

BACKGROUND: In Africa, for people with HIV on a dolutegravir-based regimen with a viral load of more than 1000 copies per mL despite enhanced adherence counselling, the appropriate course of action is uncertain. We aimed to evaluate the predicted effects of alternative antiretroviral regimen switching options in this population, including consideration of cost-effectiveness.
METHODS: We used an existing individual-based model to simulate risk and experience of HIV in 100 000 adults alive between 1989 and 2076. Using sampling of parameter values, we created 1000 setting-scenarios, reflecting the uncertainty in assumptions and a range of settings similar to those seen in eastern, central, southern, and western Africa. For each setting-scenario, we predicted the outcomes from the three alternative policies for people with sustained viral load non-suppression on a dolutegravir-containing regimen from 2026: a switch to a protease inhibitor-based regimen (switch policy), a switch to a protease inhibitor-based regimen only if HIV drug resistance testing beforehand shows integrase inhibitor resistance (resistance test policy), and no switch with no HIV drug resistance test (no switch policy). We considered predicted outcomes over 10-year and 50-year periods from 2026, used a 3% discount rate, and a cost-effectiveness threshold of US$500 per disability-adjusted life-year (DALY) averted. Ritonavir-boosted darunavir costs $210 per year, and dolutegravir less than $20. We assumed a cost of HIV drug resistance testing of $200 and considered variations around this. For comparing policies, we calculated net DALYs, which account for the health consequences of differences in costs and provide a measure of the impact of a policy on overall population burden of disease.
FINDINGS: Across setting-scenarios, there was a mean of 14 480 deaths per year (95% CI 13 750-15 210) over 50 years with a mean annual discounted cost of $103·2 million (95·8-106·5) with the switch policy in the context of having scaled to a setting with an adult population of 10 million in 2024. Compared with the switch policy, the no switch policy was predicted to lead to an overall increased number of DALYs incurred (mean 4400 per year, 95% CI 3200-5500), although it resulted in the lowest overall cost, with a difference in annual

discounted costs of $5·1 million (95% CI 4·6-5·6) lower than the switch policy. The resistance test policy led to a similar risk of death and DALYs to the switch policy at a lower overall cost (difference in annual discounted costs $3·5 million per year, 95% CI 3·1-3·9), leading to 6900 (95% CI 5500-8200) fewer net DALYs per year. Net DALYs for the resistance test versus no switch policies were similar (-1000 net DALYs, 95% CI 400 to -2300). The incremental cost-effectiveness ratio when comparing the resistance test policy with the no switch policy was $376 per DALY averted; the switch policy was dominated.
INTERPRETATION: Introduction of HIV drug resistance testing for people with sustained viral load non-suppression on dolutegravir-based antiretroviral therapy is likely to be cost-effective. We suggest that exploratory planning for increased access and scale-up of high-quality, low-cost drug resistance testing for the region is undertaken.
FUNDING: Gates Foundation as part of the HIV Modelling Consortium.

DOI: 10.1016/S2352-3018(25)00068-2
PMID: 40578374

Recent TB News

Shortened Treatment Benefits Some With Pre-Extensively Drug-Resistant TB, But Not All
https://www.cidrap.umn.edu/tuberculosis/shortened-treatment-benefits-some-pre-extensively-drug-resistant-tb-not-all

A recent multi-country randomized controlled trial demonstrated that a shortened, oral drug regimen worked well for some participants who had pre-extensively drug resistant tuberculosis (pre-XDR TB). The purpose of this study was to help contribute to evidence that shorter, oral drug regimens could help treat all forms of drug-resistant tuberculosis (DR-TB). Although it was not a perfect cure for all, it sheds light that more tailored approaches might be more necessary for these kinds of limited, DR-TB.

New TB Drugs Show Promise With Fewer Side Effects Than Linezolid
https://www.news-medical.net/news/20250708/New-TB-drugs-show-promise-with-fewer-side-effects-than-linezolid.aspx

Two peer-reviewed articles shared that the drugs sutezolid and delpazolid may have strong antimicrobial activity as well as a stronger safety profile when compared to the current treatment drug linezolid, as linezolid has some adverse effects in some patients. Moving forward, sutezolid and delpazolid may be more well tolerated for patients and become better treatments for TB.