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1. A non-randomized pragmatic historically controlled trial evaluating the effectiveness and safety of a bedaquiline or a linezolid-based short regimen for rifampicin-resistant tuberculosis.

J Infect. 2024 Oct 17:106291. doi: 10.1016/j.jinf.2024.106291. Online ahead of print.

Martínez-Campreciós J(1), Aznar ML(2), Zacarias A(3), Terán R(3), Nindia A(4), Espinosa-Pereiro J(1), Aixut S(5), Ramos ME(6), Nicolau MJ(6), Sulleiro E(7), Tórtola MT(7), Sánchez-Montalvá A(8), Molina I(1).

Author information:
(1)Infectious Diseases Department, Tropical Medicine and International Health Unit, Vall Hebron University Hospital, Barcelona, 08035 Barcelona, Spain; Centro de Investigación Biomédica en Red de Enfermedades, Infecciosas, Instituto de Salud Carlos III, Madrid, Spain.
(2)Infectious Diseases Department, Tropical Medicine and International Health Unit, Vall Hebron University Hospital, Barcelona, 08035 Barcelona, Spain; Centro de Investigación Biomédica en Red de Enfermedades, Infecciosas, Instituto de Salud Carlos III, Madrid, Spain. Electronic address: marialuisa.aznar@vallhebron.cat.
(3)Tuberculosis Unit, Hospital Nossa Senhora da Paz, Cubal, 690 Benguela, Angola.
(4)Laboratory Department, Hospital Nossa Senhora da Paz, Cubal, 690 Benguela, Angola.
(5)Infectious Diseases Department, Tropical Medicine and International Health Unit, Vall Hebron University Hospital, Barcelona, 08035 Barcelona, Spain; Tuberculosis Unit, Hospital Nossa Senhora da Paz, Cubal, 690 Benguela, Angola.
(6)National program for the control of tuberculosis, Luanda, Angola.
(7)Microbiology Department, Vall Hebron University Hospital, Barcelona, 08035 Barcelona, Spain.
(8)Infectious Diseases Department, Tropical Medicine and International Health Unit, Vall Hebron University Hospital, Barcelona, 08035 Barcelona, Spain; Centro de Investigación Biomédica en Red de Enfermedades, Infecciosas, Instituto de Salud Carlos III, Madrid, Spain; Grupo de Estudio de micobacterias, Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica, Madrid, Spain.

BACKGROUND: Short all-oral regimens for Rifampicin-resistant tuberculosis (ShORRT) have been a turning point in the treatment of drug-resistant tuberculosis. Despite this, access to drugs, stockouts, or adverse effects may

limit the use of the recommended regimens.
METHODS: Pragmatic non-randomized trial evaluating the efficacy and safety of a ShORRT strategy for the treatment of rifampicin-resistant Tuberculosis (RR-TB) at the Hospital Nossa Senhora da Paz (Angola). The strategy assigned participants to receive a bedaquiline (BDQ) or a linezolid-based (LZF) regimen supplemented with levofloxacin, clofazimine, and cycloserine for up to 9 months.
RESULTS: One hundred and twenty-one participants with pulmonary RR-TB were treated with the ShORRT strategy, 69 received the bedaquiline- and 52 the linezolid-based regimen. Overall, 98 (81%) participants had successful treatment outcomes, which was significantly higher compared to a 20-month historical injectable-based regimen (successful outcome rate including cure and treatment completed: 53.7%) ($p < 0.001$). No significant differences between treatment success rates (85.5% vs. 75.0%), treatment failure (0.0% vs. 1.9%), death (5.8% vs. 13.5%), or lost to follow-up (LTFU) (8.7% vs. 9.6%) were seen between the BDQ and the LZF-based regimen. Globally, 72 adverse events (AE) occurred in 36 (29.7%) participants. Eighteen (14.9%) of these were grade ≥ 3 and were more frequently observed in those receiving the LZD-based regimen ($p =0.02$).
CONCLUSION: The ShORRT strategy with a nine-month BDQ- or LZD-based regimen supports the efficacy of shorter all-oral regimens for the treatment of RR-TB and presents real-world data from schemes without bedaquiline, nitroimidazole, or injectables.

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2. Silicosis predicts drug resistance and retreatment among tuberculosis patients in India: a secondary data analysis from Khambhat, Gujarat (2006-2022).

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Rupani MP(1).

Author information:
(1)Clinical Epidemiology (Division of Health Sciences), ICMR - National Institute of Occupational Health (NIOH), Indian Council of Medical Research, Meghaninagar, Ahmedabad City, Gujarat, 380016, India. mihirrupani@gmail.com.

BACKGROUND: India, with the highest global burden of tuberculosis (TB) and drug-resistant TB, aims to eliminate TB by 2025. Yet, limited evidence exists on

drug resistance patterns and retreatment among patients with silico-tuberculosis. This study explores these patterns and assesses the impact of silicosis on TB retreatment in India.
METHODS: This secondary data analysis stems from a larger retrospective cohort study conducted in Khambhat, Gujarat, between January 2006 and February 2022. It included 138 patients with silico-tuberculosis and 2,610 TB patients without silicosis. Data from the Nikshay TB information portal were linked with silicosis diagnosis reports from the Pneumoconiosis Board using the unique Nikshay ID as the linking variable. Drug-resistant TB was defined as resistance to any anti-TB drug recorded in Nikshay. Retreatment refers to TB patients who have previously undergone anti-TB treatment for one month or more and need further treatment. Recurrent TB denotes patients who were previously declared cured or had completed treatment but later tested positive for microbiologically confirmed TB. Multivariable logistic regression was used to determine the impact of co-prevalent silicosis on drug resistance and retreatment.
RESULTS: Patients with silico-tuberculosis showed a higher proportion of retreatment compared to those without silicosis (55% vs. 23%, $p < 0.001$). Notably, 28% of patients with silico-tuberculosis were recurrent TB cases, compared to 11% among those without silicosis. Regarding drug resistance, the silico-tuberculosis group exhibited a higher rate (6% vs. 3%), largely due to rifampicin resistance (5% vs. 2%, $p = 0.022$). Co-prevalent silicosis was associated with a 2.5 times greater risk of drug-resistant TB (adjusted OR 2.5, 95% CI, 1.1-5.3; $p = 0.021$). Additionally, patients with silico-tuberculosis had a fourfold increased risk of retreatment for TB (adjusted OR 4, 95% CI, 3-6; $p < 0.001$).
CONCLUSIONS: Co-prevalent silicosis significantly elevates the risk of drug resistance, recurrence, and retreatment among TB patients in India. This study indicates a need for improved treatment protocols and suggests that future research should focus on randomized controlled trials to evaluate appropriate anti-TB regimen and duration of therapy for this high-risk group. Given India's goal to eliminate TB by 2025, addressing the challenges posed by silico-tuberculosis is critical.

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

3. Draft genome sequence of Mycolicibacterium conceptionense isolated from the sputum sample of a patient with pulmonary tuberculosis.

Microbiol Resour Announc. 2024 Oct 18:e0072424. doi: 10.1128/mra.00724-24. Online ahead of print.

Chauhan V(1)(2), Singh A(1), Arora R(1), Shrivastava K(1), Kathait S(1), Kumar S(2), Bhatnagar AK(3), Varma-Basil M(1).

Author information:
(1)Department of Microbiology, Vallabhbhai Patel Chest Institute, University of Delhi, Delhi, India.
(2)Department of Microbiology, Maharshi Dayanand University, Rohtak, India.
(3)Department of Chest and Tuberculosis, Rajan Babu Institute of Pulmonary Medicine and Tuberculosis, New Delhi, India.

We report the draft genome of Mycolicibacterium conceptionense, a rapidly growing nontuberculous mycobacterium, isolated from the sputum sample of a patient undergoing treatment for multidrug-resistant tuberculosis in Delhi, India. The 6,366,717-bp genome contains 6,124 coding sequences, one 5S rRNA, three 16S rRNAs, six 23S rRNAs, and 49 tRNAs.

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4. Prevalence and epidemic pattern of ecdemic multidrug-resistant tuberculosis during 2012-2022 in Hangzhou, China: implication for public health strategies.

BMC Public Health. 2024 Oct 17;24(1):2859. doi: 10.1186/s12889-024-20273-7.

Li Q(1), Wu Y(1), Cheng Q(1), Lu M(1), Huang Y(1), Bai X(1), Jia Q(1), Fang Z(1), Ai L(1), Jiang N(1), Lao Q(2), Xie L(1), Chen J(3).

Author information:
(1)Hangzhou Center for Disease Control and Prevention(Hangzhou Health Supervision Institution), 568 Mingshi Road, Hangzhou City, 310021, China.
(2)Liuzhou People's Hospital Affiliated to Guangxi Medical University, Liuzhou, China.
(3)Hangzhou Center for Disease Control and Prevention(Hangzhou Health Supervision Institution), 568 Mingshi Road, Hangzhou City, 310021, China. hzjkcjf@163.com.

BACKGROUND: To assess the prevalence and epidemic pattern of multidrug-resistant tuberculosis in Hangzhou City, Zhejiang Province, China during 2012-2022.
METHODS: All the tuberculosis cases undergoing drug susceptibility testing during 2012-2022 were included in this study. De-identified information was extracted from the electronic database Tuberculosis Information Management

System for analysis of drug resistance prevalence in Hangzhou and ecdemic multidrug-resistant tuberculosis which originated from other regions. Chi-square tests were used to compare drug resistance rates between different groups, while Chi-square tests for trend were used to evaluate the change of drug resistance rates over the years of 2012-2022. The sources and destinations of ecdemic multidrug-resistant tuberculosis were illustrated using a Sankey diagram.
RESULTS: Of 21,127 cases included in this study, 1119 (5.3%) were multidrug-resistant tuberculosis. A significant decline in multidrug-resistant tuberculosis rates was observed during 2012-2022. There was a significant difference in multidrug-resistant tuberculosis rates among immigrant population and local residents in Hangzhou City. Of 1119 multidrug-resistant tuberculosis cases, 515(46%) were ecdemic multidrug-resistant tuberculosis cases, of which 277(53.8%) were from other parts of Zhejiang Province and 238(46.2%) were from other provinces in China. Anhui, Jiangxi and Sichuan were among top three provinces which were the source of ecdemic multidrug-resistant tuberculosis cases. Three districts including Xiaoshan, Shangcheng and Linping districts had the most cases in Hangzhou. The proportion of ecdemic multidrug-resistant tuberculosis cases in Binjiang, Xiaoshan, Qiantang and Linping districtalso exceeded 30% of total cases.
CONCLUSIONS: Multidrug-resistant tuberculosis prevalence has been declining in Hangzhou. Migrant population contributed to a significant potion of cases in Hangzhou. Interventions should be tailed to local and migrant residents.

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5. Novel Treatment for Pre-XDR Tuberculosis Linked to a Lethal Case of Acute Myocarditis.

Diagnostics (Basel). 2024 Sep 26;14(19):2139. doi: 10.3390/diagnostics14192139.

Kotoulas SC(1), Poulios P(1), Chasapidou G(2), Angeloudi E(1), Bargiota T(1), Stougianni M(1), Manika K(3), Mouloudi E(1).

Author information:
(1)Adult ICU, General Hospital of Thessaloniki "Hippokration", National Healthcare System, 54642 Thessaloniki, Greece.
(2)Pulmonary Department, General Hospital of Thessaloniki "G. Papanikolaou", National Healthcare System, 57010 Thessaloniki, Greece.

(3)Adult CF Unit, Pulmonary Department, General Hospital of Thessaloniki "G. Papanikolaou", Aristotle's University of Thessaloniki, 57010 Thessaloniki, Greece.

The management of resistant tuberculosis (tb) can be extremely difficult, especially in case of novel unpredicted complications. In this report, we present a case of a 48-year-old patient with pre-extensively drug-resistant (XDR) tb who received a treatment regimen including pretomanid, bedaquiline, linezolid, cycloserine, and amikacin and died due to myocarditis. Acquired resistance to first- and second-line drugs developed due to previous poor adherence to medication. The clinical presentation of the patient, along with her initial ultrasonographical, electrocardiogram (ECG), and laboratory examinations, were typical for acute myocarditis; however, the patient was considered unstable, and further investigations, including magnetic resonance imaging (MRI), pericardiocentesis, and endomyocardial biopsy were not performed. To our knowledge, this is the first case of myocarditis in such a patient, the clinical features of which raised a high suspicion of drug induction that could be attributed to the treatment regimen that was administered. Clinicians who manage cases of drug-resistant tb should be aware of this newly reported, potentially lethal, adverse event.

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PMID: 39410543

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6. Predictors of early and interim culture un-conversion in multidrug-resistant/rifampicin-resistant tuberculosis: a retrospective multi-center cohort study in China.

Antimicrob Resist Infect Control. 2024 Oct 15;13(1):126. doi: 10.1186/s13756-024-01480-8.

Chen Q(#)(1), He W(#)(1), Du J(#)(2), Kang W(#)(3), Zou L(1), Tang X(1), Tang P(4), Guo C(5), Pan Q(6), Zhu Q(7), Yang S(8), Guo Z(1), Wu G(9), Tang S(10).

Author information:
(1)Department of Tuberculosis, Public Health Clinical Center of Chengdu, Jingjusi 18 Street, Jingjiang District, Chengdu, 610061, Sichuan, China.
(2)Department of Tuberculosis, Wuhan Pulmonary Hotel, Hubei, China.
(3)Beijing Chest Hospital, Beijing Tuberculosis and Thoracic Tumor Research Institute, Capital Medical University, Beijing, China.
(4)Department of Tuberculosis, the Fifth People's Hospital of Suzhou, Jiangsu,

China.
(5)Department of Tuberculosis, Harbin Chest Hospital, Heilongjiang, China.
(6)Department of Respiratory and Critical Care Medicine, Anqing Municipal Hospital, Anhui, China.
(7)Department of Tuberculosis, The Fourth People's Hospital of Nanning, Guangxi, China.
(8)Department of General Internal Medicine, Chongqing Public Health Medical Center, Chongqing, China.
(9)Department of Tuberculosis, Public Health Clinical Center of Chengdu, Jingjusi 18 Street, Jingjiang District, Chengdu, 610061, Sichuan, China. wuguihuicd@126.com.
(10)Beijing Chest Hospital, Beijing Tuberculosis and Thoracic Tumor Research Institute, Capital Medical University, Beijing, China. tangsj1106@vip.sina.com.
(#)Contributed equally

BACKGROUND: We aimed to evaluate the predictors for early and interim culture conversion within 2 months and 6 months of treatment in multidrug-resistant/rifampicin-resistant tuberculosis (MDR/RR-TB) patients in China.
METHODS: This study included adult MDR/RR-TB patients with a positive baseline sputum culture from 8 institutions located in different cities in China from May 2018 to January 2022. We mainly used logistic regression model to derive possible predictors of early and interim culture conversion.
RESULTS: A total of 813 patients were enrolled and 28.5% of them received multidrug-resistant treatment regimens containing bedaquiline. Of these, 362 (44.5%) patients experienced culture conversion within 2 months of treatment, and 649 (79.8%) within 6 months. The results of the multivariable logistic regression analysis revealed that acid-fast bacilli smear positive (adjusted odds ratio [aOR] = 1.637, 95% confidence interval [CI] = 1.197-2.238), cavities (aOR = 1.539, 95% CI = 1.132-2.092), bilateral disease (aOR = 1.638, 95% CI = 1.183-2.269), and viral hepatitis (aOR = 2.585, 95% CI = 1.189-5.622) were identified as risk factors for early culture un-conversion within 2 months of treatment. Additionally, smoking history (aOR = 2.197, 95% CI = 1.475-3.273), previous treatment for tuberculosis (aOR = 1.909, 95% CI = 1.282-2.844), bilateral disease (aOR = 2.201, 95% CI = 1.369-3.537), viral hepatitis (aOR = 2.329, 95% CI = 1.094-4.962) were identified as risk factors for interim culture un-conversion within 6 months of treatment, while patients with regimen containing bedaquiline (aOR = 0.310, 95% CI = 0.191-0.502) was a protective factor.
CONCLUSIONS: A history of smoking, a baseline sputum AFB smear positive, lung cavities, bilateral disease, previous anti-tuberculosis treatment, or a comorbidity of viral hepatitis can be used as the predictors for early and interim culture un-conversion in MDR/RR-TB patients, while bedaquiline was a protective factor .

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

7. Impact of Isoniazid Monoresistance on Overall and Vulnerable Patient Populations in Taiwan.

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Lee MR(1)(2), Keng LT(2), Lee MC(3)(4)(5), Chen JH(5)(6)(7), Lee CH(8)(9), Wang JY(10).

Author information:
(1)Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan.
(2)Department of Internal Medicine, National Taiwan University Hospital Hsin-Chu Branch, Hsin-Chu, Taiwan.
(3)Department of Pharmacy, New Taipei City Hospital, New Taipei City, Taiwan.
(4)School of Pharmacy, College of Pharmacy, Taipei Medical University, Taipei, Taiwan.
(5)Department of Nursing, Cardinal Tien College of Healthcare and Management, Taipei, Taiwan.
(6)Graduate Institute of Data Science, College of Management, Taipei Medical University, Taipei, Taiwan.
(7)Department of Medical Education and Research, Wanfang Hospital, Taipei Medical University, Taipei, Taiwan.
(8)Department of Internal Medicine, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan.
(9)Pulmonary Research Center, Division of Pulmonary Medicine, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan.
(10)Biostatistics Center, College of Management, Taipei Medical University, Taipei, Taiwan.

AbstractIsoniazid is an early bactericidal anti-tuberculosis (TB) agent and isoniazid mono-resistance TB is the most prevalent drug-resistant TB worldwide. Concerns exist regarding whether resistance to isoniazid would lead to delayed culture conversion and worst outcomes. From January 2008 to November 2017, adult culture-positive pulmonary TB patients receiving isoniazid, rifampicin,

pyrazinamide, and ethambutol were identified through Taiwan Center for Disease Control database and were followed until the end of 2017. Primary outcomes included time to sputum culture conversion (SCC) within two months. Secondary outcomes included death and unfavorable outcomes at the end of 2nd month. A total of 37,193 drug-susceptible and 2,832 isoniazid monoresistant pulmonary TB patients were identified. Compared with no resistance, isoniazid monoresistance was not associated with a delayed SCC (HR: 0.99, 95% CI: 0.94–1.05, p = 0.8145), a higher risk of 2-month mortality (HR: 1.19, 95% CI: 0.92–1.53, p = 0.1884), and unfavorable outcomes at 2nd month (OR: 1.05, 95% CI: 0.97–1.14, p = 0.2427). Isoniazid monoresistance was associated with delayed SCC (HR: 0.90, 95% CI: 0.83–0.98, p = 0.0099) and a higher risk of unfavorable outcomes (OR:1.18, 95% CI: 1.05–1.32, p = 0.0053) in patients aged between 20 and 65, and delayed SCC in patients without underlying comorbidities (HR: 0.90, 95% CI: 0.81–0.98, p = 0.0237). Isoniazid mono-resistant TB had a comparable outcome with drug-susceptible TB at the end of the intensive phase. Healthy, and non-elderly patients were more likely to had culture persistence, raising concerns about disease transmission in these subgroups and warranting early molecular testing for isoniazid resistance.

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PMID: 39404086

8. Risk factors for multidrug-resistant tuberculosis: a predictive model study.

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Wu L(1)(2), Cai X(3), Jiang X(2)(4).

Author information:
(1)Department of Clinical Laboratory Medicine, Wenzhou Central Hospital, The Ding Li Clinical College of Wenzhou Medical University, Wenzhou, China.
(2)Key Laboratory of Diagnosis and Treatment of New and Recurrent Infectious Diseases of Wenzhou, Wenzhou Central Hospital, The Dingli Clinical College of Wenzhou Medical University, Wenzhou, China.
(3)Department of Clinical Laboratory Medicine, Wenzhou People's Hospital, Wenzhou, China.
(4)Department of Infectious Diseases, Wenzhou Central Hospital, The Ding Li Clinical College of Wenzhou Medical University, Wenzhou, China.

OBJECTIVE: To investigate the risk factors associated with Multidrug-resistant tuberculosis (MDR-TB) in people with drug-resistant tuberculosis (DR-TB) and develop a predictive model.
METHODS: A total of 893 individuals with DR-TB treated at Wenzhou Central

Hospital from January 2018 to December 2022 were included in the study after excluding 178 individuals with incomplete clinical and laboratory data, leaving 715 individuals for analysis. Data on demographic information, baseline clinical characteristics, laboratory and imaging results, and clinical diagnosis were collected to identify the risk factors for MDR-TB and establish a predictive model.
RESULTS: Multivariate logistic regression analysis identified residence in rural areas, retreatment of TB, presence of pulmonary cavity, uric acid (UA) ≥ 346 μmol/L and c-reactive protein (CRP) < 37.3 mg/L as independent risk factors for MDR-TB in individuals with DR-TB. A nomogram model was constructed using these five factors to predict the risk of MDR-TB, with an area under the ROC curve (AUC) of 0.758 for the training group and 0.775 for the validation group. Calibration curve analysis showed good agreement between predicted and actual MDR-TB incidence in both groups, and decision curve analysis showed that the nomogram model had a higher rate of clinical net benefit.
CONCLUSION: This study suggests that residence, types of TB treatment, presence of pulmonary cavity, UA and CRP are associated with MDR-TB occurrence in individuals with DR-TB, and the nomogram model developed in this study shows promising predictive value.

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9. Impact of heteroresistance on treatment outcomes of people with drug-resistant TB.

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Crowder R(1)(2), Kato-Maeda M(1)(2), Schwem B(3), Dela Tonga A(3), Geocaniga-Gaviola DM(4), Lopez E(4), Valdez CL(4), Lim AR(4), Hunat N(5), Sedusta AG(5), Sacopon CA(5), Atienza GAM(5), Bulag E(5), Lim D(5), Bascuña J(5), Shah K(1)(2), Basillio RP(5), Berger CA(1)(2), Lopez MCDP(3), Sen S(6), Allender C(7), Folkerts M(7), Karaoz U(8), Brodie E(8), Mitarai S(9), Garfin AMC(4), Ama MC(5), Engelthaler DM(7), Cattamanchi A(1)(2)(10), Destura R(3).

Author information:

(1)Division of Pulmonary and Critical Care Medicine, San Francisco General Hospital, University of California San Francisco, San Francisco, CA, USA.
(2)Center for Tuberculosis, University of California San Francisco, San Francisco, CA, USA.
(3)University of the Philippines, National Institutes of Health, Manila, Philippines.
(4)Philippines Department of Health, Manila, Philippines.
(5)National Tuberculosis Reference Laboratory, Research Institute for Tropical Medicine, Muntinlupa, Philippines.
(6)Department of Preventive Medicine, University of Tennessee Health Science Center, Memphis, TN, USA.
(7)Pathogen and Microbiome Division, Translational Genomics Research Institute, Flagstaff, AZ, USA.
(8)Ecology Department, Lawrence Berkeley National Laboratory, Berkeley, CA, USA.
(9)Research Institute for Tuberculosis, Tokyo, Japan.
(10)Division of Pulmonary Diseases and Critical Care Medicine, University of California Irvine, Irvine, CA, USA.

BACKGROUND: Poor treatment outcomes among people with drug-resistant TB (DR-TB) are a major concern. Heteroresistance (presence of susceptible and resistant Mycobacterium tuberculosis in the same sample) has been identified in some people with TB, but its impact on treatment outcomes is unknown.
METHODS: We used targeted deep sequencing to identify mutations associated with DR-TB and heteroresistance in culture samples of 624 people with DR-TB. We evaluated the association between heteroresistance and time to unfavorable treatment outcome using Cox proportional hazards regression.
RESULTS: The proportion of drug-resistant isolates with a known mutation conferring resistance was lower for streptomycin (45.2%) and second-line injectables (79.1%) than for fluoroquinolones (86.7%), isoniazid (93.2%) and rifampin (96.5%). Fifty-two (8.3%) had heteroresistance, and it was more common for fluoroquinolones (4.6%) than rifampin (2.2%), second-line injectables (1.4%), streptomycin (1.7%), or isoniazid (1.3%). There was no association between heteroresistance and time to unfavorable outcome among people with multidrug-resistant TB (adjusted hazard ratio [aHR] 1.74, 95% CI 0.39-7.72) or pre-extensively DR-TB (aHR 0.65, 95% CI 0.24-1.72).
CONCLUSIONS: Heteroresistance was relatively common (8.3%) among people with DR-TB in the Philippines. However, we found insufficient evidence to demonstrate an impact on unfavorable treatment outcomes.

Publisher: CONTEXTE: Les résultats médiocres du traitement chez les personnes atteintes de TB résistante aux médicaments (DR-TB, pour l’anglais « drug-resistant TB ») constituent une préoccupation significative. L'hétérorésistance, caractérisée par la coexistence de souches sensibles et résistantes de Mycobacterium tuberculosis dans un même échantillon, a été

observée chez certains patients, mais les conséquences de cette situation sur l'efficacité des traitements demeurent incertaines.
MÉTHODES: Nous avons recouru au séquençage profond ciblé afin d'identifier les mutations liées à la DR-TB et à l'hétérorésistance dans les échantillons de culture provenant de 624 personnes atteintes de DR-TB. Nous avons analysé le lien entre l'hétérorésistance et le délai jusqu'à l'issue défavorable du traitement en utilisant une régression des risques proportionnels de Cox.
RÉSULTATS: La proportion d'isolats, présentant une mutation connue associée à la résistance, était inférieure pour la streptomycine (45,2%) et les médicaments injectables de deuxième ligne (79,1%) par rapport aux fluoroquinolones (86,7%), à l'isoniazide (93,2%) et à la rifampicine (96,5%). Parmi les isolats, cinquante-deux (8,3%) manifestaient une hétérorésistance, plus courante pour les fluoroquinolones (4,6%) que pour la rifampicine (2,2%), les médicaments injectables de deuxième ligne (1,4%), la streptomycine (1,7%) ou l'isoniazide (1,3%). Aucune association n'a été observée entre l'hétérorésistance et un délai d'évolution défavorable chez les patients atteints de TB multirésistante (rapport de risque ajusté [aHR] 1,74 ; IC à 95% 0,39–7,72) ou de DR-TB pré-extensive (aHR 0,65 ; IC à 95% 0,24–1,72).
CONCLUSIONS: L'hétérorésistance a été observée de manière relativement fréquente (8,3%) chez les personnes atteintes de DR-TB aux Philippines. Néanmoins, nous n'avons pas identifié de preuves suffisantes pour établir un lien avec des résultats de traitement défavorables.

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10. Identifying risk factors for recurrent multidrug resistant tuberculosis based on patient's record data from 2016 to 2021: retrospective study.

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Wotale TW(1)(2), Lelisho ME(3), Negasa BW(4), Tareke SA(5), Gobena WE(4), Amesa EG(4).

Author information:
(1)Department of Statistics, College of Natural and Computational Sciences, Dilla University, Dilla, Ethiopia. teramaj24@gmail.com.
(2)Department of Statistics, College of Natural and Computational Sciences, Mattu University, Mattu, Ethiopia. teramaj24@gmail.com.

(3)Department of Statistics, College of Natural and Computational Sciences, Mizan-Tepi University, Tepi, Ethiopia. mesfinstat27@gmail.com.
(4)Department of Statistics, College of Natural and Computational Sciences, Mattu University, Mattu, Ethiopia.
(5)Department of Statistics, College of Natural and Computational Sciences, Mizan-Tepi University, Tepi, Ethiopia.

Globally, the prevalence of multidrug-resistant tuberculosis (MDR-TB) has been increasing recently. This is a major public health concern, as MDR-TB is more difficult to treat and has poorer outcomes compared to drug-sensitive tuberculosis. The main objective of the study was to identify risk factors for recurrent multidrug-resistant tuberculosis, at Alert Specialized Hospital, Addis Ababa, by using different parametric shared frailty models. From January 2016 to December 2021, a retrospective study was conducted on MDR-TB patients at Alert Specialized Hospital in Addis Ababa. The data for the study were collected from the medical records of MDR-TB patients at the hospital during this time period. Gamma and inverse-Gaussian shared frailty models were used to analyze the dataset, with the exponential, Weibull, and lognormal distributions included as baseline hazard functions. The data were analyzed using R statistical software. The median recurrence time of the patients was 12 months, and 149 (34.3%) had recurrences. The clustering effect was statistically significant for multiple drug-resistant tuberculosis patients' recurrence. According to the Weibull-Inverse-Gaussian model, factors that reduced time to MDR-TB recurrence included lower weight (ϕ = 0.944), smoking (ϕ = 0.045), alcohol use (ϕ = 0.631), hemoptysis (ϕ = 0.041), pneumonia (ϕ = 0.564), previous anti-TB treatment (ϕ = 0.106), rural residence (ϕ = 0.163), and chronic diseases like diabetes (ϕ = 0.442) were associated with faster recurrence. While, higher education (ϕ = 3.525) and age (ϕ = 1.021) extended time to recurrence. For weight increment, smokers and alcohol users, clinical complications of hemoptysis and pneumonia, patients with pulmonary disease who had a history of previous anti-TB treatment, and being rural residents are prognostic factors. There was a significant clustering effect at the Alert Specialized Hospital in Addis Ababa, Ethiopia. The Weibull-Inverse Gaussian Shared Frailty Model was chosen as the best model for predicting the time to recurrence of MDR-TB.

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11. Drug-resistance characteristics, genetic diversity, and transmission dynamics of

multidrug-resistant or rifampicin-resistant Mycobacterium tuberculosis from 2019 to 2021 in Sichuan, China.

Antimicrob Resist Infect Control. 2024 Oct 14;13(1):125. doi: 10.1186/s13756-024-01482-6.

Gao W(1), Wang W(1), Li J(1), Gao Y(1), Zhang S(1), Lei H(1), He L(1), Li T(1), He J(2).

Author information:
(1)Sichuan Center for Disease Control and Prevention, Institute for Tuberculosis Control and Prevention, Chengdu, 610041, Sichuan, China.
(2)Sichuan Center for Disease Control and Prevention, Institute for Tuberculosis Control and Prevention, Chengdu, 610041, Sichuan, China. hejinge@163.com.

BACKGROUND: Multidrug- or rifampicin-resistant tuberculosis (TB; MDR/RR-TB) is a significant public health threat. However, the mechanisms involved in its transmission in Sichuan, China are unclear. To provide a scientific basis for MDR/RR-TB control and prevention, we investigated the drug-resistance characteristics, genetic diversity, and transmission dynamics and analyzed the demographic and clinical characteristics of patients to identify risk factors for the acquisition of MDR/RR-TB in Sichuan, Western China.
METHODS: Whole-genome sequencing was performed using a sample comprised of all MDR/RR-TB strains isolated from patients with pulmonary TB (≥ 15 years) at the 22 surveillance sites in Sichuan province between January 2019 and December 2021, to analyze genotypic drug resistance and genetic diversity. Moreover, we performed statistical analyses of the epidemiological characteristics and risk factors associated with the transmission dynamics of MDR/RR-TB.
RESULTS: The final analysis included 278 MDR/RR TB strains. Lineage 2.2, the major sub-lineage, accounted for 82.01% (228/278) of isolates, followed by lineage 4.5 (9.72%, 27/278), lineage 4.4 (6.83%, 19/278), and lineage 4.2 (1.44%, 4/278). The drug resistance rates, ranging from high to low, were as follows: isoniazid (229 [82.37%]), streptomycin (177 [63.67%]), ethambutol (144 [51.80%]), pyrazinamide (PZA, 119 [42.81%]), fluoroquinolones (FQs, 93 [33.45%]). Further, the clofazimine, bedaquiline, and delamanid resistance rates were 2.88, 2.88, and 1.04%, respectively. The gene composition cluster rate was 32.37% (90/278). In addition, 83.81% (233/278) of MDR/RR-TB cases were determined to be likely caused by transmission. Finally, patients infected with lineage two strains and strains with the KatG S315T amino acid substitution presented a higher risk of MDR/RR-TB transmission.
CONCLUSION: Transmission plays a significant role in the MDR/RR-TB burden in Sichuan province, and lineage 2 strains and strains harboring KatG S315T have a high probability of transmission. Further, high levels of FQ and PZA drug resistance suggest an urgent need for drug susceptibility testing prior to

designing therapeutic regimens. New anti-TB drugs need to be used standardly and TB strains should be regularly monitored for resistance to these drugs.

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12. HIV co-infection increases the risk of post-tuberculosis mortality among persons who initiated treatment for drug-resistant tuberculosis.

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Salindri AD(1)(2), Kipiani M(3)(4)(5), Lomtadze N(3)(4)(5), Tukvadze N(3)(6), Avaliani Z(3)(7), Blumberg HM(8)(9), Masyn KE(10), Rothenberg RB(10), Kempker RR(8), Magee MJ(11)(12).

Author information:
(1)Department of Population Health Sciences, Georgia State University School of Public Health, Atlanta, GA, USA. adsalind@stanford.edu.
(2)Division of Infectious Diseases and Geographic Medicine, Department of Medicine, Stanford University School of Medicine, Stanford, CA, USA. adsalind@stanford.edu.
(3)National Center for Tuberculosis and Lung Diseases, Tbilisi, Georgia.
(4)David Tvildiani Medical University, Tbilisi, Georgia.
(5)The University of Georgia, Tbilisi, Georgia.
(6)Department of Medicine, Swiss Tropical and Public Health Institute, Allschwil, Switzerland.
(7)European University, Tbilisi, Georgia.
(8)Division of Infectious Diseases, Department of Medicine, Emory University School of Medicine, Atlanta, GA, USA.
(9)Hubert Department of Global Health and Department of Epidemiology, Emory University Rollins School of Public Health, Atlanta, GA, USA.
(10)Department of Population Health Sciences, Georgia State University School of Public Health, Atlanta, GA, USA.
(11)Division of Infectious Diseases, Department of Medicine, Emory University School of Medicine, Atlanta, GA, USA. mjmagee@emory.edu.
(12)Hubert Department of Global Health and Department of Epidemiology, Emory University Rollins School of Public Health, Atlanta, GA, USA. mjmagee@emory.edu.

Update of

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Little is known regarding the relationship between common comorbidities in persons with tuberculosis (TB) (including human immunodeficiency virus [HIV], diabetes, and hepatitis C virus [HCV]) and post-TB mortality. We conducted a retrospective cohort study among persons who initiated treatment for rifampicin-resistant or multi/extensively drug-resistant (RR or M/XDR) TB reported to the country of Georgia's TB surveillance during 2009-2017. Exposures included HIV serologic status, diabetes, and HCV status. Our outcome was all-cause post-TB mortality determined by cross-validating vital status with Georgia's death registry through November 2019. We estimated adjusted hazard rate ratios (aHR) and 95% confidence intervals (CI) of post-TB mortality among participants with and without comorbidities using cause-specific hazard regressions. Among 1032 eligible participants, 34 (3.3%) died during treatment and 87 (8.7%) died post-TB treatment. The median time to post-TB death was 21 months (interquartile range 7-39) after TB treatment. After adjusting for confounders, the hazard rates of post-TB mortality were higher among participants with HIV co-infection (aHR = 3.74, 95%CI 1.77-7.91) compared to those without HIV co-infection. In our cohort, post-TB mortality occurred most commonly in the first 3 years post-TB treatment. Linkage to care for common TB comorbidities post-treatment may reduce post-TB mortality rates.

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13. Widespread loss-of-function mutations implicating preexisting resistance to new or repurposed anti-tuberculosis drugs.

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Conkle-Gutierrez D(1), Gorman BM(1), Thosar N(1), Elghraoui A(1), Modlin SJ(1), Valafar F(2).

Author information:
(1)Laboratory for Pathogenesis of Clinical Drug Resistance and Persistence, San Diego State University, San Diego, CA, USA.
(2)Laboratory for Pathogenesis of Clinical Drug Resistance and Persistence, San Diego State University, San Diego, CA, USA. Electronic address:

faramarz@sdsu.edu.

BACKGROUND: Five New or Repurposed Drugs (NRDs) were approved in the last decade for treatment of multi-drug resistant tuberculosis: bedaquiline, clofazimine, linezolid, delamanid, and pretomanid. Unfortunately, resistance to these drugs emerged faster than anticipated, potentially due to preexisting resistance in naïve strains. Previous investigations into the rapid emergence have mostly included short variants. For the first time, we utilize de novo-assembled genomes, and systematically include Structural Variations (SV) and heterogeneity to comprehensively study this rapid emergence. We show high prevalence of preexisting resistance, identify novel markers of resistance, and lay the foundation for preventing preexisting resistance in future drug development.
METHODS: First, a systematic literature review revealed 313 NRD resistance variants in 13 genes. Next, 409 globally diverse clinical isolates collected prior to the drugs' programmatic use (308 were multidrug resistant, 106 had de novo assembled genomes) were utilized to study the 13 genes comprehensively for conventional, structural, and heterogeneous variants.
FINDINGS: We identified 5 previously reported and 67 novel putative NRD resistance variants. These variants were 2 promoter mutations (in 8/409 isolates), 13 frameshifts (21/409), 6 SVs (9/409), 35 heterogeneous frameshifts (32/409) and 11 heterogeneous SVs (12/106). Delamanid and pretomanid resistance mutations were most prevalent (48/409), while linezolid resistance mutations were least prevalent (8/409).
INTERPRETATION: Preexisting mutations implicated in resistance to at least one NRD was highly prevalent (85/409, 21 %). This was mostly caused by loss-of-function mutations in genes responsible for prodrug activation and efflux pump regulation. These preexisting mutations may have emerged through a bet-hedging strategy, or through cross-resistance with non-tuberculosis drugs such as metronidazole. Future drugs that could be resisted through loss-of-function in non-essential genes may suffer from preexisting resistance. The methods used here for comprehensive preexisting resistance assessment (especially SVs and heterogeneity) may mitigate this risk during early-stage drug development.

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PMID: 39393282

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financial interests or personal relationships that could have appeared to influence the work reported in this paper.

14. Multiloculated thoracoabdominal tuberculosis: A radiological presentation of disseminated tuberculosis.

Radiol Case Rep. 2024 Sep 24;19(12):6302-6307. doi: 10.1016/j.radcr.2024.09.041. eCollection 2024 Dec.

Ibrahim MB(1), Shaikh RH(2), Jahangir A(2), Khan AH(3), Noor H(4).

Author information:
(1)Medical Graduate, Aga Khan University Hospital, Karachi 74800, Pakistan.
(2)Medical College, Aga Khan University, Karachi 74800, Pakistan.
(3)Medical College, Sahara Medical College, Narowal, Pakistan.
(4)Medical College, Fatima Jinnah Medical University, Lahore.

Tuberculosis is more frequently found among high-risk populations in the United States. It has a challenging diagnosis since it can present with diverse organ involvement that may delay the diagnosis. This is especially true regarding hepatic tuberculosis, with prevalence varying in each study but highly suggestive of underdiagnosis. An 18-year-old male with high-risk exposure to multidrug-resistant tuberculosis presented with fever, night sweats, weight loss, and cough. Imaging revealed a right lung cavitary mass with bilateral pulmonary nodules, right pleural nodular thickening traversing diaphragm extending to the liver with subcapsular hepatic lobulated hypodensities. MRI showed spinal involvement consistent with Pott's disease. It is important to consider hepatic tuberculosis in differential diagnoses for a hepatic lesion, allowing early detection and treatment to optimize patient outcomes.

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PMID: 39387022

15. Extracorporeal membrane oxygenation for tuberculosis-related acute respiratory distress syndrome: An international multicentre retrospective cohort study.

Crit Care. 2024 Oct 9;28(1):332. doi: 10.1186/s13054-024-05110-y.

Ait Hssain A(1), Petit M(2), Wiest C(3), Simon L(4), Al-Fares AA(5), Hany A(6), Garcia-Gomez DI(7), Besa S(8), Nseir S(9), Guervilly C(10), Alqassem W(11),

Lesouhaitier M(12), Chelaru A(13), Sin SW(14), Roncon-Albuquerque R Jr(15), Giani M(16)(17), Lepper PM(18), Lavillegrand JR(19), Park S(20), Schellongowski P(21), Fawzy Hassan I(1), Combes A(22), Sonneville R(13), Schmidt M(23)(24); TB ECMO study group.

Author information:
(1)Medical Intensive Care Unit, Hamad General Hospital, Department of Medicine, Weill Cornell Medical College Doha, College of Health and Life Science, Hamad Bin Khalifa University, Doha, Qatar.
(2)Medical Intensive Care Unit, Ambroise Paré Hospital, APHP, Inserm U1018, CESP, University Versailles Saint Quentin - University Paris Saclay, Guyancourt, France.
(3)Department of Internal Medicine II, University Hospital of Regensburg, Regensburg, Germany.
(4)Department of Critical Care, Guy's and St Thomas' NHS Foundation Trust, London, UK.
(5)Department of Anesthesia, Critical Care Medicine, and Pain Medicine, Al-Amiri Center for Advanced Respiratory and Cardiac Failure, Al-Amiri Hospital, Ministry of Health, Kuwait City, Kuwait.
(6)Intensive Care Unit-Al-Adan Hospital, Ministry of Health-Kuwait, Kuwait City, Kuwait.
(7)Fundacion Cardiovascular de Colombia, Bucaramanga, Colombia.
(8)Division of Surgery, Department of Cardiac Surgery, Pontificia Universidad Católica de Chile, Santiago, Chile.
(9)Médecine Intensive-Réanimation, CHU de Lille et Inserm U1285, Université de Lille, CNRS, UMR 8576 - UGSF, 59000, Lille, France.
(10)Center for Studies and Research on Health Services and Quality of Life EA3279, Aix-Marseille University, Service de Medecine Intensive et Reanimation, CHU Hopital Nord, Assistance Publique Hôpitaux de Marseille (APHM), Marseille, France.
(11)Critical Care Department, Prince Mohammed Bin Abdulaziz Hospital, Riyadh, Saudi Arabia.
(12)Infectious Diseases and Intensive Care Unit, Pontchaillou University Hospital, 2 rue Henri Le Guilloux, UMR 1236, Univ Rennes, INSERM, Etablissement Français du Sang Bretagne, Rennes, France.
(13)INSERM U1137, APHP.Nord, Médecine intensive - réanimation, Hôpital Bichat - Claude Bernard, Université Paris Cité, Paris, France.
(14)The University of Hong Kong, Hong Kong, China.
(15)Department of Intensive Care Medicine, São João University Hospital, Porto, Portugal.
(16)Department of Medicine and Surgery, University of Milano-Bicocca, Monza, Italy.
(17)Department of Emergency and Intensive Care, Fondazione IRCCS San Gerardo dei Tintori, Monza, Italy.

(18)Department of Pneumology, Allergology and Critical Care Medicine, Department of Emergency Medicine, University Hospital of Saarland and University of Saarland, Homburg, Germany.
(19)Medical Intensive Care Unit, Henri Mondor Hospital, Creteil, France.
(20)Department of Pulmonary, Allergy and Critical Care Medicine, Hallym University Sacred Heart Hospital, Anyang 14068, South Korea.
(21)Department of Medicine I, Intensive Care Unit 13i2, Medical University of Vienna, Vienna, Austria.
(22)Sorbonne Université, GRC 30 RESPIRE, UMRS_1166-ICAN, Institute of Cardiometabolism and Nutrition, Sorbonne Université, 75013, Paris, France.
(23)Sorbonne Université, GRC 30 RESPIRE, UMRS_1166-ICAN, Institute of Cardiometabolism and Nutrition, Sorbonne Université, 75013, Paris, France. matthieu.schmidt@aphp.fr.
(24)Medical Intensive Care Unit, Assistance Publique-Hôpitaux de Paris, Pitié-Salpêtrière Hospital, 47-83 Boulevard de l'Hôpital, 75013, Paris, France. matthieu.schmidt@aphp.fr.

OBJECTIVE: To report the outcomes of patients with severe tuberculosis (TB)-related acute respiratory distress syndrome (ARDS) on extracorporeal membrane oxygenation (ECMO), including predictors of 90-day mortality and associated complications.
METHODS: An international multicenter retrospective study was conducted in 20 ECMO centers across 13 countries between 2002 and 2022.
RESULTS: We collected demographic data, clinical details, ECMO-related complications, and 90-day survival status for 79 patients (median APACHE II score of 20 [25th to 75th percentile, 16 to 28], median age 39 [28 to 48] years, PaO2/FiO2 ratio of 69 [55 to 82] mmHg before ECMO) who met the inclusion criteria. Thoracic computed tomography showed that 61 patients (77%) had cavitary TB, while 18 patients (23%) had miliary TB. ECMO-related complications included major bleeding (23%), ventilator-associated pneumonia (41%), and bloodstream infections (32%). The overall 90-day survival rate was 51%, with a median ECMO duration of 20 days [10 to 34] and a median ICU stay of 42 days [24 to 65]. Among patients on VV ECMO, those with miliary TB had a higher 90-day survival rate than those with cavitary TB (90-day survival rates of 81% vs. 46%, respectively; log-rank P = 0.02). Multivariable analyses identified older age, drug-resistant TB, and pre-ECMO SOFA scores as independent predictors of 90-day mortality.
CONCLUSION: The use of ECMO for TB-related ARDS appears to be justifiable. Patients with miliary TB have a much better prognosis compared to those with cavitary TB on VV ECMO.

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16. A modified BPaL regimen for tuberculosis treatment replaces linezolid with inhaled spectinamides.

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Zohaib Ali M(1)(2)(3), Dutt TS(1)(2), MacNeill A(2), Walz A(1)(2), Pearce C(1)(2)(3), Lam H(1)(2), Philp JS(1)(2), Patterson J(1)(2), Henao-Tamayo M(1)(2), Lee R(4), Liu J(4), Robertson GT(1)(2), Hickey AJ(5), Meibohm B(6), Gonzalez Juarrero M(1)(2).

Author information:
(1)Mycobacteria Research Laboratories, Colorado State University, Fort Collins, United States.
(2)Microbiology, Immunology and Pathology, Colorado State University, Fort Collins, United States.
(3)Program in Cell & Molecular Biology, Colorado State University, Fort Collins, United States.
(4)Department of Chemical Biology and Therapeutics, St. Jude Children's Research Hospital, Memphis, United States.
(5)Technology Advancement and Commercialization, RTI International, Research Triangle Park, United States.
(6)Department of Pharmaceutical Sciences, University of Tennessee Health Science Center, Memphis, United States.

Update of
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The Nix-TB clinical trial evaluated a new 6 month regimen containing three oral drugs; bedaquiline (B), pretomanid (Pa), and linezolid (L) (BPaL regimen) for the treatment of tuberculosis (TB). This regimen achieved remarkable results as almost 90% of the multidrug-resistant or extensively drug-resistant TB

participants were cured but many patients also developed severe adverse events (AEs). The AEs were associated with the long-term administration of the protein synthesis inhibitor linezolid. Spectinamide 1599 is also a protein synthesis inhibitor of Mycobacterium tuberculosis with an excellent safety profile, but it lacks oral bioavailability. Here, we propose to replace L in the BPaL regimen with spectinamide (S) administered via inhalation and we demonstrate that inhaled spectinamide 1599, combined with BPa --BPaS regimen--has similar efficacy to that of the BPaL regimen while simultaneously avoiding the L-associated AEs. The BPaL and BPaS regimens were compared in the BALB/c and C3HeB/FeJ murine chronic TB efficacy models. After 4-weeks of treatment, both regimens promoted equivalent bactericidal effects in both TB murine models. However, treatment with BPaL resulted in significant weight loss and the complete blood count suggested the development of anemia. These effects were not similarly observed in mice treated with BPaS. BPaL and BPa, but not the BPaS treatment, also decreased myeloid to erythroid ratio suggesting the S in the BPaS regimen was able to recover this effect. Moreover, the BPaL also increased concentration of proinflammatory cytokines in bone marrow compared to mice receiving BPaS regimen. These combined data suggest that inhaled spectinamide 1599 combined with BPa is an effective TB regimen without L-associated AEs.

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17. Multidrug-resistant tuberculosis of spine diagnosis and management: An institutional experience of 21 cases.

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Bhosale S(1), Ariwala DM(1), Phupate A(1), Marathe N(2), Seshadri H(3), Sheth U(1).

Author information:
(1)Department of Orthopedics, G.S Medical College and KEM Hospital, Mumbai, Maharashtra, India.
(2)Synapse Spine, Kaul Heritage city,Vasai, Palghar, Maharashtra, India.
(3)Department of Radiology, G.S Medical College and KEM Hospital, Mumbai, Maharashtra, India.

BACKGROUND: We aimed to establish a standardized protocol for managing multidrug-resistant (MDR) spinal tuberculosis (TB), addressing the surgical options, ranging from computed tomography-guided biopsy to intraoperative sampling.
METHODS: This study developed a treatment/management protocol based on an analysis of clinical, radiological, and postoperative outcomes for 21 patients with spinal MDR-TB. Over 24 months, 21 patients with multidrug-resistant spinal TB underwent the following testing: erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), numerical rating scale (NRS), and the American Spinal Injury Association Scale. Radiological criteria were based upon a comparison of preoperative and 6-month to 2-year postoperative plain radiographs.
RESULTS: The 21 patients underwent guided biopsies (35%) or intraoperative sampling (65%). For the surgical cases, dorsal vertebrae were most frequently involved (75%), and 90% underwent posterior surgical procedures. Postoperatively, ESR, CRP, kyphosis angle, and NRS score were significantly reduced. The 3 MDR patients who failed treatment were transitioned to the extensively drug-resistant (XDR) protocol wherein bedaquiline, linezolid, cycloserine, and clofazimine were given after drug sensitivity testing drug regimen, needed no further surgery, and none exhibited additional neurological deterioration.
CONCLUSION: Regular clinical, laboratory, radiological, and outcome analysis is vital for following MDR spinal TB patients; early detection of relatively rare treatment failures (i.e., 3/21 patients in this series) allows for prompt initiation of XDR treatment, resulting in better outcomes.

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18. Bedaquiline versus injectable containing regimens for rifampicin-resistant and multidrug-resistant tuberculosis in a reference center in Brazil - a real-world evidence study using a retrospective design.

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Santos AP(1), Benace CJ Jr(2), de Medeiros Leung JA(2), Kritski AL(2), de Queiroz Mello FC(2).

Author information:

(1)Thorax Diseases Institute, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil. anapsantos.ip@gmail.com.
(2)Thorax Diseases Institute, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil.

BACKGROUND: Drug resistance (DR) is one of the several challenges to global tuberculosis (TB) control. The implementation of bedaquiline (BED) for DR-TB after more than 40 years was expected to improve treatment outcomes as well as microbiologic conversion and adverse events (AE) occurrence.
METHODS: Retrospective cohort study based on secondary data of patients with rifampicin-resistant (RR) or multidrug-resistant (MDR) TB reported to the Outpatient Clinic of Mycobacterial Diseases of the Thorax Diseases Institute - Federal University of Rio de Janeiro - Brazil, between 2016 and 2023. We aimed to evaluate microbiologic conversion, AE and TB treatment outcomes and compare them according to the treatment regimen used for RR/MDR-TB patients under routine conditions [Injectable Containing Regimens (ICR) versus BED Containing Regimens (BCR)]. Logistic regression and survival analysis using Cox regression and Kaplan Meier curve were used for statistical analysis.
RESULTS: Of the 463 DR-TB patients notified during the study period, 297 (64.1%) were included for analysis (ICR = 197 and BCR = 100). Overall AEs were more frequent (83.7 vs. 16.3%, $p < 0.001$) and occurred earlier in the ICR group (15 days vs. 65 days, $p = 0.003$). There were no cases of cardiotoxicity requiring interruption of BED treatment. None of the regimens of treatment tested were associated with smear or culture conversion on Cox regression analysis ($p = 0.60$ and 0.88, respectively). BED-containing regimens were also associated with favorable outcomes in multivariable logistic regression [adjusted odds ratio (aOR) = 2.63, 95% confidence interval (CI)1.36-5.07, $p = 0.004$], as higher years of schooling, primary drug resistance, and no previous TB treatment. In the survival analysis, BCR was inversely associated with the occurrence of AE during treatment follow-up (aHR 0.24, 95% CI 0.14-0.41, $p < 0.001$). In addition, TB treatment regimens with BED were also associated with favorable outcomes (aHR 2.41, 95% CI 1.62-3.57, $p < 0.001$), along with no illicit drug use and primary drug resistance.
CONCLUSIONS: The implementation of a fully oral treatment for RR/MDR-TB in a reference center in Brazil was safe and associated with favorable outcomes under routine conditions, despite social, demographic, and behavioral factors that may influence TB treatment completion.

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

19. Isoniazid resistance pattern among pulmonary tuberculosis patients in Bangladesh: an exploratory study.

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Rahman SMM(1), Samina P(2), Rahman T(1), Sikder Adel AS(1), Nasrin R(1), Mafij Uddin MK(1), Hasan MJ(1), Ahmed S(1), Daru P(1), Modak PK(3), Hamid Salim MA(4), Ibna Mohsin SM(5), Banu S(6).

Author information:
(1)Infectious Diseases Division, icddr,b Dhaka, 1212, Bangladesh.
(2)Centre for Health Economics and Policy Analysis (CHEPA), McMaster University, Ontario, Canada.
(3)National Tuberculosis Control Programme, Bangladesh.
(4)USAID STAR Program, National Tuberculosis Control Programme, Bangladesh.
(5)U.S. Agency for International Development (USAID), Bangladesh.
(6)Infectious Diseases Division, icddr,b Dhaka, 1212, Bangladesh. Electronic address: sbanu@icddrb.org.

OBJECTIVES: In high TB burden countries like Bangladesh, research and policies tend to focus on rifampicin (RIF)-resistant TB patients, leaving RIF sensitive but isoniazid (INH) resistant (Hr-TB) patients undiagnosed. Our study aims to determine the prevalence of INH resistance among pulmonary TB (PTB) patients in selected healthcare facilities in Bangladesh.
METHODS: This study was conducted across nine TB Screening and Treatment Centers situated in Bangladesh. Sputum samples from 1084 Xpert-positive PTB patients were collected between April 2021 and December 2022, and cultured for drug susceptibility testing (DST). Demographic and clinical characteristics of Hr-TB and drug-susceptible TB patients were compared.
RESULTS: Among available DST results of 998 culture positive isolates, resistance rate of any INH regardless of RIF susceptibility was 6.4% (64/998, 95% CI, 4.9-8.2). The rate was significantly higher in previously treated (21.1%, 16/76, 95% CI, 12.0-34.2) compared to newly diagnosed TB patients (5.2%, 48/922, 95% CI, 3.8-6.9) (p <0.001). The rate of Hr-TB was 4.5% (45/998, 95% CI, 3.3-6.0), which was also higher among previously treated (6.6%, 5/76, 95% CI, 1.4-13.5) compared to newly diagnosed TB patients (4.3%; 40/922, 95% CI, 3.1-5.9) (p=0.350). Most importantly, the rate of Hr-TB was more than double compared to MDR-TB (4.5%, 45/998, vs 1.9%, 19/998) found in the current study.
CONCLUSIONS: This study reveals a high prevalence of Hr-TB, surpassing even that of the MDR-TB in Bangladesh. This emphasizes the urgent need to adopt WHO-recommended molecular tools at the national level for rapid detection of INH

resistance so that patients receive timely and appropriate treatment.

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20. Comparison of Nucleotide MALDI-TOF MS with Xpert MTB/RIF for Rifampicin Susceptibility Identification and Associated Risk Factors of Rifampicin Resistance Among Drug Resistant Mycobacterium tuberculosis.

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Song S(#)(1), Xu H(#)(1), Cao J(#)(2), Wu G(2), Sun H(1), Dai X(1), Li X(1), Chen M(1), Zhang M(1), Yan Y(1), Tong J(3), Wang Z(1).

Author information:
(1)Institute of Tuberculosis Control, Qingdao Preventive Medicine Research Institute, Qingdao Municipal Center for Disease Control and Prevention, Qingdao, People's Republic of China.
(2)Department of Laboratory Medicine, Qingdao Chest Hospital, Qingdao, Shandong, People's Republic of China.
(3)Department of Medical Affairs, Shanghai Conlight Medical Co., Ltd., Shanghai, People's Republic of China.
(#)Contributed equally

PURPOSE: Nucleotide-based matrix-assisted laser desorption ionization time-of-flight mass spectrometry (nucleotide MALDI-TOF MS) is an emerging molecular technology used for the diagnosis of tuberculosis (TB) caused by Mycobacterium tuberculosis (MTB)and its drug resistance. This study aimed to compare the ability of nucleotide MALDI-TOF MS to detect rifampicin (RIF) resistance in drug-resistant TB (DR-TB) patients with Xpert MTB/RIF and to analyze the disparate results individually. Additionally, potential factors associated with rifampicin resistance among DR-TB patients in Qingdao were investigated.
PATIENTS AND METHODS: A retrospective study was conducted at Qingdao Chest Hospital, and patients with DR-TB were enrolled. Corresponding frozen isolates were recovered and subjected to nucleotide MALDI-TOF MS, Xpert MTB/RIF, and phenotypic drug susceptibility testing (pDST). Sanger sequencing was performed for the discordant results of nucleotide MALDI-TOF MS and Xpert MTB/RIF. Univariate and multivariate logistic regression analyses were used to identify potential factors associated with rifampicin resistance among patients with DR-TB.

RESULTS: A total of 125 patients with DR-TB (18.8%, 125/668) were enrolled in this study from May 1 to July 31, 2023. Rifampicin-resistant (DR-TB/RR, 29) and rifampicin-sensitive (DR-TB/RS, 96) groups were divided according to the pDST results. Nucleotide MALDI-TOF MS performed better than Xpert MTB/RIF in terms of sensitivity, specificity, accuracy, and agreement with pDST. Only six cases had inconsistent results, and the sequencing results of five cases were identical to nucleotide MALDI-TOF MS. Furthermore, chest pain (aOR=12.84, 95% CI, 2.29-91.97, p=0.005), isoniazid sensitivity (aOR=0.14, 0.02-0.59, p=0.013), and ethambutol sensitivity (aOR=0.02, 0.00-0.10, p=0.000) were potential factors associated with rifampicin resistance among DR-TB patients in Qingdao.
CONCLUSION: The overall concordance between nucleotide MALDI-TOF MS and Xpert MTB/RIF was 95.2%, with the former performing better in determining rifampicin susceptibility among DR-TB cases in Qingdao. Chest pain, isoniazid, and ethambutol resistance might be factors associated with RIF resistance among patients with DR-TB in Qingdao.

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PMID: 39364078

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21. Discovery of benzo[c]phenanthridine derivatives with potent activity against multidrug-resistant Mycobacterium tuberculosis.

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Liang YC(#)(1)(2), Sun Z(#)(2), Lu C(#)(3)(4), Lupien A(#)(5)(6)(7)(8), Xu Z(3)(4), Berton S(2), Xu P(1), Behr MA(5)(6)(7)(8), Yang W(3)(4)(9), Sun J(1)(2).

Author information:
(1)Department of Microbiology and Immunology, University of British Columbia, Vancouver, Canada.
(2)Department of Biochemistry, Microbiology and Immunology, University of Ottawa, Ottawa, Canada.
(3)Chinese Academy of Sciences Key Laboratory of Receptor Research, Shanghai Institute of Materia Medica (SIMM), Chinese Academy of Sciences, Shanghai, China.
(4)University of Chinese Academy of Sciences, Beijing, China.

(5)Infectious Diseases and Immunity in Global Health Program, Research Institute of the McGill University Health Centre, Montréal, Canada.
(6)McGill International TB Centre, Montréal, Canada.
(7)Department of Microbiology and Immunology, McGill University, Montréal, Canada.
(8)Department of Medicine, McGill University Health Centre, Montréal, Canada.
(9)School of Pharmaceutical Science and Technology, Hangzhou Institute for Advanced Study, University of Chinese Academy of Sciences, Hangzhou, China.
(#)Contributed equally

Mycobacterium tuberculosis (Mtb), the pathogen responsible for tuberculosis (TB), is the leading cause of bacterial disease-related death worldwide. Current antibiotic regimens for the treatment of TB remain dated and suffer from long treatment times as well as the development of drug resistance. As such, the search for novel chemical modalities that have selective or potent anti-Mtb properties remains an urgent priority, particularly against multidrug-resistant (MDR) Mtb strains. Herein, we design and synthesize 35 novel benzo[c]phenanthridine derivatives (BPDs). The two most potent compounds, BPD-6 and BPD-9, accumulated within the bacterial cell and exhibited strong inhibitory activity (MIC90 ~2 to 10 µM) against multiple Mycobacterium strains while remaining inactive against a range of other Gram-negative and Gram-positive bacteria. BPD-6 and BPD-9 were also effective in reducing Mtb survival within infected macrophages, and BPD-9 reduced the burden of Mycobacterium bovis BCG in the lungs of infected mice. The two BPD compounds displayed comparable efficacy to rifampicin (RIF) against non-replicating Mtb (NR-Mtb). Importantly, BPD-6 and BPD-9 inhibited the growth of multiple MDR Mtb clinical isolates. Generation of BPD-9-resistant mutants identified the involvement of the Mmr efflux pump as an indirect resistance mechanism. The unique specificity of BPDs to Mycobacterium spp. and their efficacy against MDR Mtb isolates suggest a potential novel mechanism of action. The discovery of BPDs provides novel chemical scaffolds for anti-TB drug discovery.IMPORTANCEThe emergence of drug-resistant tuberculosis (TB) is a serious global health threat. There remains an urgent need to discover new antibiotics with unique mechanisms of action that are effective against drug-resistant Mycobacterium tuberculosis (Mtb). This study shows that novel semi-synthetic compounds can be derived from natural compounds to produce potent activity against Mtb. Importantly, the identified compounds have narrow spectrum activity against Mycobacterium species, including clinical multidrug-resistant (MDR) strains, are effective in infected macrophages and against non-replicating Mtb (NR-Mtb), and show anti-mycobacterial activity in mice. These new compounds provide promising chemical scaffolds to develop potent anti-Mtb drugs of the future.

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22. Transmission of multidrug-resistant tuberculosis in Jiangxi, China, and associated risk factors.

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Zhan J(#)(1), Wang W(#)(1)(2), Luo D(1), Chen Q(1), Yu S(1)(2), Yan L(3), Chen K(1).

Author information:
(1)Department of Clinical Laboratory, The First Affiliated Hospital, Jiangxi Medical College, Nanchang University, Nanchang, China.
(2)School of Public Health, Jiangxi Medical College, Nanchang University, Nanchang, China.
(3)Department of Clinical Laboratory, Jiangxi Provincial Chest Hospital, Nanchang, China.
(#)Contributed equally

In order to effectively combat the urgent threat of multidrug-resistant tuberculosis (MDR-TB), it is imperative to gain a comprehensive understanding of the drug-resistant profiles, transmission dynamics, and associated risk factors. Our study encompassed a population-based retrospective analysis with 130 MDR-TB patients from 2018 to 2021. The research methodology incorporated whole-genome sequencing, drug susceptibility testing , and logistic regression analysis to discern the risk factors of genomic clustering linked to recent transmission. The findings from phenotypic drug resistance assessments revealed notable resistance rates: ethambutol at 62.3% (81/130), streptomycin at 72.3% (94/130), levofloxacin at 51.5% (67/130), and moxifloxacin at 50.0% (65/130). Furthermore, among all patients, 38 individuals (29.23%, 38/130) were found to be part of 17 clusters, indicating instances of recent MDR-TB transmission. The genomic clustering patients were deeply investigated. Lineage 2.2.1 was established as the primary sub-lineage (86.15%, 112/130), followed by lineage 4 (9.23%, 12/130). Moreover, the logistic regression analysis underscored that unemployment, farming occupations, and prior TB treatment were identified as significant risk factors for recent transmission.
IMPORTANCE: The high prevalence of multidrug-resistant tuberculosis (MDR-TB) in Jiangxi Province highlights the importance of understanding the genetic background and drug resistance patterns of these strains. This knowledge is crucial for developing effective control methods. Furthermore, in light of the significance of preventing transmission among tuberculosis patients, whole-genome sequencing was utilized to investigate the recent transmission of MDR-TB and identify associated risk factors. The findings revealed that individuals in the farming sector, those who are unemployed, and patients with a

history of tuberculosis treatment are at elevated risk. Consequently, targeted public interventions for these at-risk groups are imperative.

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23. Efficacy and safety of shorter multidrug-resistant or rifampicin-resistant tuberculosis regimens: a network meta-analysis.

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Abraham Y(1), Assefa DG(2), Hailemariam T(3), Gebrie D(4), Debela DT(5), Geleta ST(6), Tesfaye D(3), Joseph M(3), Manyazewal T(3).

Author information:
(1)College of Health Sciences, Center for Innovative Drug Development and Therapeutic Trials for Africa (CDT-Africa), Addis Ababa University, P.O. Box 9086, Addis Ababa, Ethiopia. yismay7@gmail.com.
(2)Department of Nursing, College of Medicine and Health Science, Dilla University, Dilla, Ethiopia.
(3)College of Health Sciences, Center for Innovative Drug Development and Therapeutic Trials for Africa (CDT-Africa), Addis Ababa University, P.O. Box 9086, Addis Ababa, Ethiopia.
(4)College of Health Science and Medicine, Department of Pharmacy, Woldia University, Woldia, Ethiopia.
(5)Quality Improvement Unit, Shenen Gibe General Hospital, Jimma, Ethiopia.
(6)Redat Health Care, Addis Ababa, Ethiopia.

BACKGROUND: Drug-resistant tuberculosis (DR-TB) remains a threat to public health. Shorter regimens have been proposed as potentially valuable treatments for multidrug or rifampicin resistant tuberculosis (MDR/RR-TB). We undertook a systematic review and network meta-analysis to evaluate the efficacy and safety of shorter MDR/RR-TB regimens.
METHODS: We searched PubMed/MEDLINE, Cochrane Center for Clinical Trials (CENTRAL), Scopus, ClinicalTrials.gov, WHO International Clinical Trials Registry Platform, US Food and Drug Administration, and Chinese Clinical Trial Registry for primary articles published from 2013 to July 2023. Favorable (cured and treatment completed) and unfavorable (treatment failure, death, loss to follow-up, and culture conversion) outcomes were assessed as the main efficacy outcomes, while adverse events were assessed as the safety outcomes. The network meta-analysis was performed using R Studio version 4.3.1 and the Netmeta package. The study protocol adhered to the PRISMA-NMA guidelines and was registered in PROSPERO (CRD42023434050).
RESULT: We included 11 eligible studies (4 randomized control trials and 7

cohorts) that enrolled 3,548 patients with MDR/RR-TB. Treatment with a 6-month combination of BdqLzdLfxZTrd/Eto/H had two times more favorable outcomes [RR 2.2 (95% CI 1.22, 4.13), P = 0.0094], followed by a 9-11 month combination of km/CmMfx/LfxPtoCfzZEHh [RR1.67 (95% CI 1.45, 1.92), P < 0.001] and a 6-month BdqPaLzdMfx [RR 1.64 (95% CI 1.24, 2.16), P < 0.0005] compared to the standard longer regimens. Treatment with 6 months of BdqPaLzdMfx [RR 0.33 (95% CI 0.2, 0.55), P < 0.0001] had a low risk of severe adverse events, followed by 6 months of BdqPaLzd [RR 0.36 (95% CI 0.22, 0.59), P ≤ 0.001] and BdqPaLzdCfz [RR 0.54 (95% CI 0.37, 0.80), P < 0.0001] than standard of care.
CONCLUSION: Treatment of patients with RR/MDR-TB using shorter regimens of 6 months BdqLzdLfxZTrd/Eto/H, 9-11 months km/CmMfx/LfxPtoCfzZEHh, and 6 months BdqPaLzdMfx provides significantly higher cure and treatment completion rates compared to the standard longer MDR/RR-TB. However, 6BdqPaLzdMfx, 6BdqPaLzd, and 6BdqPaLzdCfz short regimens are significantly associated with decreased severity of adverse events. The findings are in support of the current WHO-recommended 6-month shorter regimens.

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24. A novel hematological score (HS) and its related nomogram model to predict nontuberculous mycobacterial pulmonary disease in patients with suspected multidrug-resistant pulmonary tuberculosis.

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Yu Q(1)(2)(3)(4), Hu S(1)(2)(3)(4), Liu F(1)(2)(3)(4), Gong F(1)(2)(3)(4).

Author information:
(1)Department of Infectious Diseases, Wuhan Jinyintan Hospital, Tongji Medical College of Huazhong University of Science and Technology, Wuhan, China.
(2)Hubei Clinical Research Center for Infectious Diseases, Wuhan, China.
(3)Wuhan Research Center for Communicable Disease Diagnosis and Treatment, Chinese Academy of Medical Sciences, Wuhan, China.
(4)Joint Laboratory of Infectious Diseases and Health, Wuhan Institute of Virology and Wuhan Jinyintan Hospital, Chinese Academy of Sciences, Wuhan, China.

BACKGROUND: Nontuberculous mycobacteria pulmonary disease (NTM-PD) exhibits clinical and radiological characteristics similar to those of pulmonary tuberculosis (PTB). This study aimed to develop a novel hematological score (HS) and its related nomogram model to identify NTM-PD in patients with suspected multidrug-resistant pulmonary tuberculosis (SMDR-PTB) due to lack of response to first-line anti-TB treatment (ATT).
METHODS: We retrospectively recruited patients with SMDR-PTB from Wuhan Jinyintan Hospital between January 2014 and January 2022. These patients were divided into NTM-PD and MDR-PTB groups based on pathogen test results. Participants were randomly allocated to training and validation set in a 7:3 ratio. The ROC and LASSO regression were employed to select variables. Multivariate logistic analysis was conducted on the training set to develop the HS and its related nomogram models, followed by internal validation on the validation set.
RESULTS: The HS was constructed and developed on CKMB, ADA, GGT, LDL, and UHR, demonstrating good predictive value with AUCs of 0.900 and 0.867 in the training and validation sets, respectively. The HS-based nomogram model consists of Age, Gender, DM, HIV infection, ILD and HS, and exhibited strong discriminative ability, accuracy, and clinical utility in two sets. The AUCs were 0.930 and 0.948 in the training set and validation set, respectively.
CONCLUSION: HS may be a useful biomarker for identifying NTM-PD in patients with SMDR-PTB. The HS-based nomogram model serves as a convenient and efficient tool for guiding the treatment of SMDR-PTB patients.

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25. A Mixed-Method Study of Medication-Related Burden Among Multi-Drug Resistant Tuberculosis Patients in West Java, Indonesia.

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Ausi Y(1), Yunivita V(2), Santoso P(3)(4), Sunjaya DK(5), Barliana MI(1)(6), Ruslami R(2).

Author information:
(1)Department of Biological Pharmacy, Faculty of Pharmacy, Universitas Padjadjaran, Sumedang, West Java, Indonesia.
(2)Division of Pharmacology and Therapy, Department of Biomedical Sciences,

Faculty of Medicine, Universitas Padjadjaran, Bandung, West Java, Indonesia.
(3)Division of Pulmonary and Critical Care, Department of Internal Medicine, Faculty of Medicine, Universitas Padjadjaran, Bandung, West Java, Indonesia.
(4)Hasan Sadikin General Hospital, Bandung, West Java, Indonesia.
(5)Department of Public Health, Faculty of Medicine, Universitas Padjadjaran, Bandung, West Java, Indonesia.
(6)Center of Excellence for Pharmaceutical Care Innovation, Universitas Padjadjaran, Bandung, West Java, Indonesia.

BACKGROUND: Multidrug-resistant tuberculosis presents a challenging obstacle in global TB control. It necessitates complex and long-term therapy, which can potentially lead to medication-related burdens that may ultimately reduce therapy adherence and quality of life.
PURPOSE: This study aimed to gain a deep understanding of the medication-related burdens experienced by multidrug-resistant tuberculosis patients.
METHODS: The study was conducted using a convergent mixed-method approach involving MDR-TB patients and their caregivers. Qualitative data were collected through semi-structured in-depth interviews, while quantitative data were gathered using the validated Living with Medicine Questionnaire 3. In the quantitative part, associations between patients' characteristics and burden levels were analysed using bivariate and multivariate analyses.
RESULTS: Seventy-four participants were involved in the study, with 71 of them completing the questionnaire and 36 participating in interviews. The qualitative results revealed the subjectivity of medication-related burden perception, which could not be fully captured by the quantitative method. Four themes of medication-related burdens emerged: personal beliefs, regimen burdens, socioeconomic burdens, and healthcare burdens. The quantitative results provided a generalized representation of the population. Age and side effects were found to be significantly associated with higher burden levels, with those aged 18-30 having an odds ratio (OR) of 7.303 (95% CI: 1.045-51.034), and those aged 31-40 having an OR of 6.53 (95% CI: 1.077-39.607). Additionally, experiencing side effects had a substantial impact, with an OR of 46.602 (95% CI: 2.825-768.894). Both sets of results are valuable for designing patient-centered care.
CONCLUSION: MDR-TB therapy imposes a significant burden, particularly regarding the characteristics of regimen. By understanding this burden, healthcare professionals can help improve the quality of life for these patients.

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PMID: 39345348

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26. Deciphering the possible role of MmpL7 efflux pump in SQ109 resistance in Mycobacterium tuberculosis.

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Jing W(#)(1), Zhang F(#)(2)(3), Shang Y(#)(2), Shi W(1), Yao C(2), Zhang X(2), Chu N(4), Lu J(5), Yuan J(6).

Author information:
(1)Department of Tuberculosis, Beijing Chest Hospital, Capital Medical University, Beijing Thoracic Tumor Research Institute, No. 9, Beiguan Street, Tongzhou District, Beijing, 101149, PR China.
(2)Department of Bacteriology and Immunology, Beijing Chest Hospital, Capital Medical University, Beijing Tuberculosis & Thoracic Tumor Research Institute, No. 9, Beiguan Street, Tongzhou District, Beijing, 101149, PR China.
(3)Department of Epidemiology, School of Public Health, Cheeloo College of Medicine, Shandong University, Jinan, 250012, PR China.
(4)Department of Tuberculosis, Beijing Chest Hospital, Capital Medical University, Beijing Thoracic Tumor Research Institute, No. 9, Beiguan Street, Tongzhou District, Beijing, 101149, PR China. chunaihui1994@sina.com.
(5)Beijing Key Laboratory for Pediatric Diseases of Otolaryngology, Head and Neck Surgery, Beijing Pediatric Research Institute, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing, 101149, PR China. lujiebch@163.com.
(6)Department of Bacteriology and Immunology, Beijing Chest Hospital, Capital Medical University, Beijing Tuberculosis & Thoracic Tumor Research Institute, No. 9, Beiguan Street, Tongzhou District, Beijing, 101149, PR China. yuanjinfeng0920@163.com.
(#)Contributed equally

BACKGROUND: SQ109 is a promising candidate drug for the treatment of patients with drug-resistant tuberculosis (DR-TB). The purpose of this study was to investigate the activity of SQ109 against clinical isolates of Mycobacterium tuberculosis (MTB) from patients with multidrug-resistant TB (MDR-TB) and pre-extensively drug-resistant TB (pre-XDR-TB), and to explore new drug-resistant mechanisms of SQ109.
METHODS: We evaluated the in vitro activity of SQ109 against clinical isolates from patients with MDR-TB and pre-XDR-TB using minimal inhibitory concentration (MIC) assay. The drug-resistant gene, mmpL3 of SQ109-resistant strains was sequenced, and a quantitative real-time PCR assay was used to analyze 28 efflux

pump genes in SQ109-resistant strains without mmpL3 mutations. The role of candidate efflux pumps mmpL5 and mmpL7 on the MIC of SQ109 was evaluated using recombinantly cloned MmpL5 and MmpL7 expressed in Mycobacterium smegmatis.
RESULTS: The MIC90, MIC95 and MIC99 values of SQ109 for 225 clinical isolates of MTB were 0.25 mg/L, 0.5 mg/L and 1.0 mg/L, respectively. Among the pre-XDR strains, six showed resistance to SQ109 despite the absence of gene mutations in mmpL3. In six resistant pre-XDR strains, the MIC of SQ109 decreased with the use of an efflux pump inhibitor, and there was significant upregulation of mmpL5 and mmpL7 in two strains after exposure to SQ109. The presence of MmpL7 in Mycobacterium smegmatis resulted in decreased susceptibility to SQ109, with the MIC increasing from 16 mg/L to 32 mg/L.
CONCLUSIONS: Our data demonstrated that SQ109 exhibited excellent levels of in vitro activity against MTB. MmpL7 may be a potential gene for MTB resistance to SQ109, providing a useful target for detecting SQ109 resistance in MTB.

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27. Evaluation and application of population pharmacokinetic models for optimising linezolid treatment in non-adherence multidrug-resistant tuberculosis patients.

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Li R(1), Sun F(1), Feng Z(1), Zhang Y(1), Lan Y(2), Yu H(3), Li Y(4), Mao J(5), Zhang W(6).

Author information:
(1)Department of Infectious Diseases, Shanghai Key Laboratory of Infectious Diseases and Biosafety Emergency Response, National Medical Centre for Infectious Diseases, Huashan Hospital, Fudan University, Shanghai, China.
(2)Department of Infectious Diseases, Shanghai Key Laboratory of Infectious Diseases and Biosafety Emergency Response, National Medical Centre for Infectious Diseases, Huashan Hospital, Fudan University, Shanghai, China; Department of Tuberculosis, Affiliated Hospital of Zunyi Medical University, Guizhou, China.
(3)Department of Infectious Diseases, Hunan University of Medicine General Hospital, Huaihua, Hunan, 418000, China.
(4)Department of Infectious Diseases, Shanghai Key Laboratory of Infectious

Diseases and Biosafety Emergency Response, National Medical Centre for Infectious Diseases, Huashan Hospital, Fudan University, Shanghai, China. Electronic address: lalaliy@sina.com.
(5)Department of Pharmacy, Huashan Hospital, Fudan University, Shanghai, 200040, China. Electronic address: jmao12@fudan.edu.cn.
(6)Department of Infectious Diseases, Shanghai Key Laboratory of Infectious Diseases and Biosafety Emergency Response, National Medical Centre for Infectious Diseases, Huashan Hospital, Fudan University, Shanghai, China; National Clinical Research Centre for Aging and Medicine, Huashan Hospital, Fudan University, Shanghai, China; Key Laboratory of Medical Molecular Virology (MOE/MOH), Shanghai Medical College, Fudan University, Shanghai, China.

BACKGROUND: Population pharmacokinetic (popPK) models can optimise linezolid dosage regimens in patients with multidrug-resistant tuberculosis (MDR-TB); however, unknown cross-centre precision and poor adherence remain problematic. This study aimed to assess the predictive ability of published models and use the most suitable model to optimise dosage regimens and manage compliance.
METHODS: One hundred fifty-eight linezolid plasma concentrations from 27 patients with MDR-TB were used to assess the predictive performance of published models. Prediction-based metrics and simulation-based visual predictive checks were conducted to evaluate predictive ability. Individualised remedial dosing regimens for various delayed scenarios were optimised using the most suitable model and Monte Carlo simulations. The influence of covariates, scheduled dosing intervals, and patient compliance were assessed.
RESULTS: Seven popPK models were identified. Body weight and creatinine clearance were the most frequently identified covariates influencing linezolid clearance. The model with the best performance had a median prediction error (PE%) of -1.62 %, median absolute PE of 29.50 %, and percentages of PE within 20 % (F20, 36.97 %) and 30 % (F30, 51.26 %). Monte Carlo simulations indicated that a twice-daily 300 mg linezolid dose may be more efficient than 600 mg once daily. For the 'typical' patient treated with 300 mg twice daily, half the dosage should be taken after a delay of ≥ 3 h.
CONCLUSIONS: Monte Carlo simulations based on popPK models can propose remedial regimens for delayed doses of linezolid in patients with MDR-TB. Model-based compliance management patterns are useful for balancing efficacy, adverse reactions, and resistance suppression.

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the submitted work in the previous three years, and no other relationships or activities that could appear to have influenced the submitted work. The authors declare no conflicts of interest.

28. Cellular and Molecular Network Characteristics of TARM1-Related Genes in Mycobacterium tuberculosis Infections.

Int J Mol Sci. 2024 Sep 20;25(18):10100. doi: 10.3390/ijms251810100.

Peng L(1), Wu H(1), Zhu L(1), Song J(1), Ma W(1), Zhong L(1), Ma W(1), Yang R(1), Huang X(1), Li B(1)(2), Luo S(1), Bao F(1)(2), Liu A(1)(2).

Author information:
(1)Yunnan Province Key Laboratory of Children's Major Diseases Research, School of Basic Medical Sciences, Kunming Medical University, Kunming 650500, China.
(2)Yunnan Provincial Key Laboratory of Public Health and Biosafety, School of Public Health, Kunming Medical University, Kunming 650500, China.

Tuberculosis (TB) is a global infectious threat, and the emergence of multidrug-resistant TB has become a major challenge in eradicating the disease that requires the discovery of new treatment strategies. This study aimed to elucidate the immune infiltration and molecular regulatory network of T cell-interacting activating receptors on myeloid cell 1 (TARM1)-related genes based on a bioinformatics analysis. The GSE114911 dataset was obtained from the Gene Expression Omnibus (GEO) and screened to identify 17 TARM1-related differentially expressed genes (TRDEGs). Genes interacting with the TRDEGs were analyzed using a Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis. A gene set enrichment analysis (GSEA) was used to identify the biological pathways significantly associated with a Mycobacterium tuberculosis (Mtb) infection. The key genes were obtained based on Cytoscape's cytoHubba plug-in. Furthermore, protein-protein interaction (PPI) networks were analyzed through STRING, while mRNA-RNA-binding protein (RBP) and mRNA-transcription factor (TF) interaction networks were developed utilizing the StarBase v3.0 and ChIPBase databases. In addition, the diagnostic significance of key genes was evaluated via receiver operating characteristic (ROC) curves, and the immune infiltration was analyzed using an ssGSEA and MCPCounter. The key genes identified in the GSE114911 dataset were confirmed in an independent GSE139825 dataset. A total of seventeen TRDEGs and eight key genes were obtained in a differential expression analysis using the cytoHubba plug-in. Through the GO and KEGG analysis, it was found that these were involved in the NF-κB, PI3K/Akt, MAPK, and other pathways related to inflammation and energy metabolism. Furthermore, the ssGSEA and MCPCounter analysis revealed a significant rise in activated T cells and T helper cells within the Mtb infection group, which were markedly associated with these key genes. This

implies their potential significance in the anti-Mtb response. In summary, our results show that TRDEGs are linked to inflammation, energy metabolism, and immune cells, offering fresh insights into the mechanisms underlying TB pathogenesis and supporting further investigation into the possible molecular roles of TARM1 in TB, as well as assisting in the identification of prospective diagnostic biomarkers.

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29. Epidemiological characteristics, diagnosis and treatment effect of rifampicin-resistant pulmonary tuberculosis (RR-PTB) in Guizhou Province.

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Zhou J(1)(2), Li J(3), Hu Y(4), Li S(5)(6).

Author information:
(1)School of Public Health, the Key Laboratory of Environmental Pollution Monitoring and Disease Control, Ministry of Education, Guizhou Medical University, No.9 Beijing Road, Yunyan District, Guiyang city, 550025, Guizhou Province, China.
(2)Guizhou Center for Disease Control and Prevention, No.73, Bageyan Road, Yunyan District, Guiyang city, 550004, Guizhou Province, China.
(3)Guizhou Center for Disease Control and Prevention, No.73, Bageyan Road, Yunyan District, Guiyang city, 550004, Guizhou Province, China. lijinlanpublic@126.com.
(4)School of Public Health, the Key Laboratory of Environmental Pollution Monitoring and Disease Control, Ministry of Education, Guizhou Medical University, No.9 Beijing Road, Yunyan District, Guiyang city, 550025, Guizhou Province, China. huyong1979@gmc.edu.cn.
(5)School of Public Health, the Key Laboratory of Environmental Pollution Monitoring and Disease Control, Ministry of Education, Guizhou Medical University, No.9 Beijing Road, Yunyan District, Guiyang city, 550025, Guizhou Province, China. zjumedjun@163.com.
(6)Guizhou Center for Disease Control and Prevention, No.73, Bageyan Road, Yunyan District, Guiyang city, 550004, Guizhou Province, China. zjumedjun@163.com.

BACKGROUND: Rifampicin-resistant pulmonary tuberculosis (RR-PTB) presents a significant threat to global public health security. China bears a substantial

burden of RR-PTB cases globally, with Guizhou Province experiencing particularly alarming trends, marked by a continual increase in patient numbers. Understanding the population characteristics and treatment modalities for RR-PTB is crucial for mitigating morbidity and mortality associated with this disease.
METHODS: We gathered epidemiological, diagnostic, and treatment data of all RR-PTB cases recorded in Guizhou Province from January 1, 2017 to December 31, 2023. Utilizing composition ratios as the analytical metric, we employed Chi-square tests to examine the spatiotemporal distribution patterns of RR-PTB patients and the evolving trends among different patient classifications over the study period.
RESULTS: In our study, 3396 cases of RR-PTB were analyzed, with an average age of 45 years. The number of RR-PTB patients rose significantly from 176 in 2017 to 960 in 2023, peaking notably among individuals aged 23-28 and 44-54, with a rising proportion in the 51-80 age group ($P < 0.001$). Since 2021, there has been a notable increase in the proportion of female patients. While individuals of Han ethnic group comprised the largest group, their proportion decreased over time ($P < 0.001$). Conversely, the Miao ethnicity showed an increasing trend ($P < 0.05$). The majority of patients were farmers, with their proportion showing an upward trajectory ($P < 0.001$), while students represented 4.33% of the cases. Geographically, most patients were registered in Guiyang and Zunyi, with a declining trend ($P < 0.001$), yet household addresses primarily clustered in Bijie, Tongren, and Zunyi. The proportion of floating population patients gradually decreased, alongside an increase in newly treated patients and those without prior anti-tuberculosis therapy. Additionally, there was a notable rise in molecular biological diagnostic drug sensitivity (real-time PCR and melting curve analysis) ($P < 0.001$). However, the cure rate declined, coupled with an increasing proportion of RR-PTB patients lost to follow-up and untreated ($P < 0.05$).
CONCLUSIONS: Enhanced surveillance is crucial for detecting tuberculosis patients aged 23-28 and 44-54 years. The distribution of cases varies among nationalities and occupations, potentially influenced by cultural and environmental factors. Regional patterns in RR-PTB incidence suggest tailored prevention and control strategies are necessary. Despite molecular tests advances, challenges persist with low cure rates and high loss to follow-up. Strengthening long-term management, resource allocation, and social support systems for RR-PTB patients is essential.

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30. Phenotypic and genotypic analysis of drug resistance in M. tuberculosis isolates in Gansu, China.

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Peng Y(1), Li C(1), Hui X(2), Huo X(3), Shumuyed NA(4), Jia Z(1)(5).

Author information:
(1)Gansu Agricultural University, Lanzhou, Gansu, China.
(2)Lanzhou Maternal and Child Health Care Hospital, Lanzhou, Gansu, China.
(3)The Third People's Hospital of Lanzhou City, Lanzhou, Gansu, China.
(4)Lanzhou Veterinary Research Institute, Chinese Academy of Agricultural Sciences, Lanzhou, Gansu, China.
(5)The Second People's Hospital of Lanzhou City, Lanzhou, Gansu, China.

Tuberculosis has posed a serious threat to human health. It is imperative to investigate the geographic prevalence of tuberculosis and medication resistance, as this information is essential for informing strategies for its prevention and treatment. Drug resistance was identified using a proportion method. Drug-resistant genes and pathways were predicted using whole genome sequencing. The drug resistance range of bedaquiline was identified using the microporous plate two-fold dilution method, and drug resistance genes were studied using sequencing. The study revealed that 19.99% of the tuberculosis cases had multidrug resistance. The genes of M. tuberculosis are predominantly involved in the synthesis of ABC transporters, two-component systems, and bacterial secretion systems, as well as in energy production and conversion, and lipid transport and metabolism. The genes encode for 82.45% of carbohydrate-related enzymes such as glycoside hydrolases, glycosyl transferases, and carbohydrate esterases. The minimum inhibitory concentration (MIC) of bedaquiline against clinical strains was approximately 0.06 μg/mL, with identified mutations in drug-resistant genes Rv0678, atpE, and pepQ, specifically V152A, P62A, and T222N, respectively. The multidrug resistance tuberculosis development was attributed to the strong medication resistance exhibited. It was concluded that tuberculosis had presented a high level of drug resistance. Phenotypic resistance was related to genes, existing potential genetic resistance in M. tuberculosis. Bedaquiline was found to possess effective antibacterial properties against M. tuberculosis.

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31. Prevalence, treatment, and outcomes of hepatitis C in an MDR/RR-TB trial cohort.

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Jansen van Vuuren J(1), Crocker-Buque T(2), Berry C(1), Viatushka D(3), Usmanova R(4), Nyang'wa BT(1), Parpieva N(3), Liverko I(3), Solodovnikova V(4), Sinha A(1).

Author information:
(1)Médecins sans Frontières, United Kingdom & Netherlands.
(2)London School of Hygiene & Tropical Medicine, London, United Kingdom.
(3)Belarus Republican Specialized Scientific Practice Medical Center of Phthisiology and Pulmonology, Minsk, Belarus.
(4)Republican Scientific and Practical Centre for Pulmonology and Tuberculosis, Tashkent, Uzbekistan.

Tuberculosis (TB) and chronic hepatitis C virus infection (HCV) remain significant global health challenges, especially in low- and middle-income countries. In Eastern Europe, a considerable percentage of multi-drug resistant (MDR) and rifampicin resistant (RR) TB populations show high HCV prevalence. Current WHO guidelines do not routinely advise HCV testing during MDR-TB treatment, despite HCV being a risk factor for drug-induced liver complications in TB patients. This study investigates the co-treatment of MDR/RR-TB and HCV, using data from the TB-PRACTECAL trial. Data were collected as part of the TB-PRACTECAL clinical trial. All participants were screened for HCV at baseline. Participants who were HCV antibody positive and those who were treated for hepatitis C with Direct Acting Antivirals (DAAs) were extracted and compared to overall cohort characteristics. The characteristics of participants concomitantly treated with direct-acting antivirals are described including hepatitis treatment outcomes and adverse events. Among 552 participants from Belarus, Uzbekistan, and South Africa, 24 (4.3%) were HCV antibody positive. Unfavourable TB treatment outcomes were noted in 106/523 (22%) of the HCV-negative, 8/18 (44%) of the HCV-seropositive, and 2/7 (29%) of HCV-confirmed participants treated with DAAs. Of the six participants who received concurrent

HCV and MDR/RR TB treatment, three were cured of HCV and three had no post-treatment HCV RNA test, five completed TB treatment and one discontinued treatment due to a severe adverse reaction. Concurrent treatment of MDR-TB and HCV, including in HIV patients, showed promising outcomes with no significant adverse events. The findings support the potential benefits of integrating HCV care into MDR-TB management.

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32. Accessibility of TB diagnostic services at primary healthcare clinics in the eThekwini district, South Africa: a geospatial analysis.

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Dlangalala T(1), Musekiwa A(2), Mckelly D(3), Baloyi E(4), Mashamba-Thompson TP(2)(5).

Author information:
(1)School of Health Systems and Public Health, Faculty of Health Sciences University of Pretoria Private Bag, Pretoria, South Africa u10225120@tuks.co.za.
(2)School of Health Systems and Public Health, Faculty of Health Sciences University of Pretoria Private Bag, Pretoria, South Africa.
(3)CSIR, Cape Town, Inclusive Smart Settlements and Regions (ISSR) Central, South Africa.
(4)Ekurhuleni Metropolitan Municipality, Germiston, Gauteng, South Africa.
(5)Faculty of Health Sciences University of Pretoria, Pretoria, South Africa.

BACKGROUND: Improving geographic access can aid in managing tuberculosis (TB) by enabling early diagnosis and treatment initiation. Although geospatial techniques have been used to map the transmission patterns of drug-resistant TB in South Africa, fewer studies have investigated the accessibility of TB diagnostic services. This study evaluated the accessibility of TB diagnostic services and disease distribution in the eThekwini district of South Africa.

METHODS: In this cross-sectional study, population data for 2021 were disaggregated into smaller analysis units and then re-aggregated through the dasymetric mapping technique. Data on notified TB patients, including Global Positioning System coordinates of clinics, were obtained from the District of Health Information System, exported to ArcGIS 10.8.2 and used to calculate distances to the nearest clinics and hospitals.
RESULTS: 92% of the population (3 730 494 people) in eThekwini could access TB diagnostic services within 5 km. Patients travelled an average distance of 4.7 km (range: 0.1-26.9 km). TB diagnostic services were highly accessible in the Northern and Central regions and moderately accessible in the predominately rural Western and Southern regions. The smallest population of eThekwini resides in rural areas; however, 40.7% of its residents live >5 km from a diagnosing facility, with patients in the South having to travel up to 44.5 km. TB incidence was higher in the predominately rural West and South regions compared with the Central and North regions which are mainly comprised of urban and suburban areas. Our findings also showed that 98.4% of the clinics in eThekwini were located within 30 km of a hospital at an average distance of 9.6 km within the district. However, the distribution of these hospitals does not demonstrate equitable access as the majority are located within the Central region, and fewer are found in the other three regions of eThekwini.
CONCLUSIONS: Addressing the disparities in access to TB diagnostic services is required in the eThekwini district. Leveraging the existing mobile health clinics can assist with this, particularly, in rural areas with inadequate access. Additionally, active-case finding should be intensified in these regions since they had a higher TB burden per population. Prioritising interventions in these areas is crucial for reducing the impact of the disease on affected communities.

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33. Response to treatment and low serum vitamin D levels in North Indian patients with treatment-naive category I and multi-drug resistant pulmonary tuberculosis.

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Rathored J(1)(2), Sharma SK(1), Banavaliker JN(3), Sreenivas V(4), Srivastava

AK(5).

Author information:
(1)Department of Medicine, All India Institute of Medical Sciences, New Delhi, India.
(2)Department of 'School of Allied Health Sciences', Datta Meghe Institute of Higher Education and Research, Wardha, Maharashtra, India.
(3)Department of Tuberculosis and Respiratory Diseases, Rajan Babu Institute of Pulmonary Medicine and Tuberculosis (RBIPMT), New Delhi, India.
(4)Department of Biostatistics, All India Institute of Medical Sciences, New Delhi, India.
(5)Department of Laboratory Medicine, All India Institute of Medical Sciences, New Delhi, India.

BACKGROUND: Tuberculosis (TB) is a bacterial infection that usually affects the lungs, although it can also affect other parts of the body. Vitamin D deficiency and response to treatment have been demonstrated in patients with active TB in several studies, but not in MDR-TB patients, which is a new observation in the present study.
OBJECTIVE: To study the time to initial sputum culture conversion and to associate baseline vitamin D levels and response to treatment in patients with PTB Cat I and MDR-TB.
METHODS: A total of 897 North Indian participants were recruited and divided into three groups: treatment-naïve PTB Cat I, MDR-TB, and healthy controls. Serum biochemistry, including 25-hydroxyvitamin D and calcium, was measured in all participants with PTB, Cat I, and MDR-TB.
RESULTS: PTB Cat I patients had high bacillary load grading at baseline compared to 2nd month followed by 6th month of treatment. More severe chest radiographic features, such as cavitation and the presence of bilateral disease at baseline. Mean sputum smear conversion times were 0.95 ± 0.7 months and culture conversion to negative occurred at a mean time of 0.8 ± 0.7 in PTB Cat I patients compared to MDR-TB patients on average sputum smear and time of 2.4 ± 3 months. Significantly lower mean serum 25-hyroxyvitamin D concentration was found in the 6th month than in the 2nd month and baseline in PTB Cat I.
CONCLUSION: Low serum vitamin D deficiency was observed in both groups during treatment and is one of the important factors responsible for susceptibility to TB in both groups; however, its significance is uncertain. Patients with continuous positive sputum for multidrug-resistant tuberculosis (MDR-TB) had a worse prognosis than those with sputum bacteriology conversion. Two months into a treatment regimen, sputum smear conversions may be a useful indicator of an MDR-TB patient's prognosis.

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34. Association of bacteriomes with drug susceptibility in lesions of pulmonary tuberculosis patients.

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Du W(1), Zhao Y(1), Zhang C(1), Zhang L(1), Zhou L(1), Sun Z(1), Huang X(1), Zhang N(1), Liu Z(1), Li K(1), Che N(1).

Author information:
(1)Department of Pathology, Beijing Key Laboratory for Drug Resistant Tuberculosis Research, Beijing Chest Hospital, Capital Medical University, Beijing Tuberculosis and Thoracic Tumor Research Institute, Beiguandajie 9#, Tongzhou Dist, Beijing, 101149, China.

Understanding how the bacteriomes in tuberculous lesions can be influenced by the susceptibility of Mycobacterium tuberculosis (MTB) can provide valuable information for preventing and treating drug resistant tuberculosis (DR-TB). High-throughput 16S rRNA sequencing was employed to analyze the bacteriome in pulmonary TB lesions from 14 patients with DR-TB and 47 patients with drug sensitive tuberculosis (DS-TB), along with 18 normal lung tissues (NT) from 18 lung cancer patients serving as the bacterial baseline. The phylogenetic investigation of communities by reconstruction of unobserved states2 (PICRUSt2) algorithm was utilized to predict bacterial metabolic functions. The major phyla of pulmonary bacteriomes included Proteobacteria, Actinobacteria, Bacteroidetes, Firmicutes and Fusobacteria. Alpha diversity indices, including ACE, Chao1, Shannon and OTU observed, all demonstrated different bacterial communities of DS-TB samples from that of NT samples; while only Shannon indicated difference between DR-TB and NT samples. The analysis of similarity (ANOSIM) showed significantly different bacterial communities within TB lesions compared to NT samples ($R = 0.418$, $p = 0.001$). However, difference was not observed between DR-TB and DS-TB samples (ANOSIM, $R = 0.069$, $p = 0.173$). The bacterial profiles within each DR-TB individual appeared unique, with no obvious clusters corresponding to drug-resistant phenotypes. Nevertheless, indicator genera identified in DR-TB and DS-TB lesions demonstrated distinctive micro-ecological environments. Most COG functions were enriched in TB lesions, and the most significant one was [J] translation, ribosomal structure and biogenesis. The distinct enrichment patterns of bacterial enzymes in DR-TB and DS-TB lesions suggest that pulmonary bacterial activities can be modulated by the

susceptibility of MTB bacilli. This study provides fresh perspectives and strategies for the precise diagnosis and assessment of drug resistance tuberculosis.

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35. Diagnostic Accuracy of BD MAX MDR-TB Assay Performed on Bronchoscopy Specimens in Patients with Suspected Pulmonary Tuberculosis.

Tuberc Respir Dis (Seoul). 2024 Sep 23. doi: 10.4046/trd.2024.0091. Online ahead of print.

Ko SJ(1), Yoon KH(2).

Author information:
(1)Department of Internal Medicine, Wonkwang University Sanbon Hospital, Gunpo, Republic of Korea.
(2)Department of Laboratory Medicine, Wonkwang University Sanbon Hospital, Gunpo, Republic of Korea.

BACKGROUND: Several novel molecular platforms using nucleic acid amplification tests have been developed for the diagnosis of pulmonary tuberculosis (PTB) and rapid detection of isoniazid and rifampin resistance. Among them, the BD MAX MDR-TB assay (BD MAX) has shown high sensitivity and specificity; however, its diagnostic accuracy performed on bronchoscopy specimens has not been reported.
METHODS: We retrospectively reviewed the medical records of patients with suspected PTB who underwent bronchoscopy. Patients who underwent BD MAX testing of bronchoscopy specimens were included in the final analysis. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for PTB diagnosis were calculated using a positive culture of Mycobacterium tuberculosis as the reference standard.
RESULTS: Of 114 patients, 34 had culture-confirmed PTB. The sensitivity, specificity, PPV, and NPV of BD MAX performed on bronchoscopy specimens for the diagnosis of PTB were 79.4%, 88.8%, 75.0%, and 91.0%, respectively. The sensitivity of BD MAX was superior to that of acid-fast bacillus smear (79.4% vs. 38.2%, $p < 0.001$).
CONCLUSION: BD MAX performed on bronchoscopy specimens showed high accuracy for

diagnosing PTB. BD MAX can be performed on bronchoscopy specimens in patients with suspected PTB.

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PMID: 39308277

36. Clinical profiles of multidrug-resistant and rifampicin-monoresistant tuberculosis in Korea, 2018-2021: a nationwide cross-sectional study.

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Min J(1), Ko Y(2), Kim HW(3), Koo HK(4), Oh JY(5), Jeon D(6), Lee T(7), Kim YC(8), Lim SC(9), Lee SS(4), Park JS(10), Kim JS(3).

Author information:
(1)Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea.
(2)Division of Pulmonary, Allergy and Critical Care Medicine, Department of Internal Medicine, Kangdong Sacred Heart Hospital, Hallym University College of Medicine, Seoul, Republic of Korea.
(3)Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Incheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea.
(4)Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Ilsan Paik Hospital, Inje University College of Medicine, Goyang, Republic of Korea.
(5)Division of Pulmonary, Allergy, and Critical Care Medicine, Department of Internal Medicine, Korea University Guro Hospital, Korea University College of Medicine, Seoul, Republic of Korea.
(6)Department of Internal Medicine, Pusan National University Yangsan Hospital, Pusan National University School of Medicine, Yangsan, Republic of Korea.
(7)Division of Respiratory and Critical Care Medicine, Department of Internal Medicine, Ulsan University Hospital, University of Ulsan College of Medicine, Ulsan, Republic of Korea.
(8)Department of Internal Medicine, Chonnam National University Medical School, and Chonnam National University Hwasun Hospital, Hwasun, Jeonnam, Republic of Korea.
(9)Department of Internal Medicine, Chonnam National University, Gwanju, Republic of Korea.
(10)Division of Pulmonology, Department of Internal Medicine, Dankook University College of Medicine, Cheonan, Republic of Korea.

BACKGROUND: This study aimed to identify the clinical characteristics of multidrug-resistant/rifampicin-resistant tuberculosis (MDR/RR-TB) in the Republic of Korea.
METHODS: Data of notified people with tuberculosis between July 2018 and December 2021 were retrieved from the Korea Tuberculosis Cohort database. MDR/RR-TB was further categorized according to isoniazid susceptibility as follows: (1) MDR-TB, (2) rifampicin-monoresistant tuberculosis (RMR-TB), and (3) RR-TB if susceptibility to isoniazid was unknown. Multivariable logistic regression analysis was conducted to identify the factors associated with MDR/RR-TB.
RESULTS: Between 2018 and 2021, the proportion of MDR/RR-TB cases among all TB cases and TB cases with known drug susceptibility test results was 2.1% (502/24,447). The proportions of MDR/RR-TB and MDR-TB cases among TB cases with known drug susceptibility test results were 3.3% (502/15,071) and 1.9% (292/15,071), respectively. Among all cases of rifampicin resistance, 31.7% (159/502) were RMR-TB and 10.2% (51/502) were RR-TB. Multivariable logistic regression analyses revealed that younger age, foreigners, and prior tuberculosis history were significantly associated with MDR/RR-TB.
CONCLUSION: Rapid identification of rifampicin resistance targeting the high-risk populations, such as younger generations, foreign-born individuals, and previously treated patients are necessary for patient-centered care.

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PMID: 39308276

37. Psychosocial experiences of adolescents with tuberculosis in Cape Town.

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Wademan DT(1), Mlomzale M(1), Marthinus AJ(1), Jacobs S(1), Mcimeli K(1), Zimri K(1), Seddon JA(1)(2), Hoddinott G(1)(3).

Author information:
(1)Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa.
(2)Department of Infectious Disease, Imperial College London, London, United Kingdom.
(3)School of Public Health, Faculty of Medicine and Health, The University of Sydney, Sydney, Australia.

Adolescents (10-19-years-old) account for almost 10% of the annual global tuberculosis (TB) incidence. Adolescents' experiences of TB care, TB stigma, and

the consequences of TB for their relationships, schooling, and mental health are different, and often more severe, compared to younger children and adults. How TB impacts the lives of adolescents is not well described or understood. We aimed to locate adolescents' experiences of TB relative to their psychosocial contexts, describe the impact of TB on adolescents' wellbeing, and describe how TB and its treatment affects their socio-familial contexts. Teen TB was a prospective observational cohort study which recruited 50 adolescents with newly diagnosed TB disease (including both multidrug-resistant TB and drug-susceptible TB) in Cape Town, South Africa. A nested sub-sample of 20 adolescents were purposively sampled for longitudinal qualitative data collection. Nineteen participants completed all qualitative data collection activities between December 2020 and September 2021. Adolescents described their communities as undesirable places to live-rife with violence, poverty, and unemployment. The negative experiences of living in these conditions were exacerbated by TB episodes among adolescents or within their households. TB and its treatment disrupted adolescents' socio-familial connections; many participants described losing friendships and attachment to family members as people reacted negatively to their TB diagnosis. TB, inclusive of the experience of disease, diagnosis and treatment also negatively impacted adolescents' mental health. Participants reported feeling depressed, despondent, and at times suicidal. TB also disrupted adolescents' schooling and employment opportunities as adolescents were absent from school and college for substantial periods of time. Our findings confirm that adolescents' psychosocial experiences of TB are often highly negative, compounding underlying vulnerability. Future research should prioritize exploring the potential of social protection programmes providing adolescents and their families with psychosocial and economic support.

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38. Critical assessment of infants born to mothers with drug resistant tuberculosis.

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Loveday M(1)(2)(3), Gandhi NR(4), Khan PY(5)(6), Theron G(7), Hlangu S(1), Holloway K(8), Chotoo S(8), Singh N(8), Marais BJ(9)(10).

Author information:
(1)HIV and Other Infectious Diseases Research Unit (HIDRU), South African Medical Research Council, Durban, South Africa.
(2)CAPRISA-MRC HIV-TB Pathogenesis and Treatment Research Unit, Durban, South Africa.
(3)Centre for Health Systems Research & Development, University of the Free State, South Africa.
(4)Rollins School of Public Health and Emory School of Medicine, Emory University, Atlanta, USA.
(5)London School of Hygiene and Tropical Medicine, London, UK.
(6)Africa Health Research Institute, Durban, South Africa.
(7)DSI-NRF Centre of Excellence for Biomedical Tuberculosis Research, 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.
(8)King Dinuzulu Hospital Complex, Sydenham, Durban, South Africa.
(9)WHO Collaborating Centre for Tuberculosis, Sydney Infectious Diseases Institute, University of Sydney, Sydney, NSW, Australia.
(10)The Children's Hospital at Westmead, Sydney, NSW, Australia.

BACKGROUND: There have been no detailed descriptions of infants born to mothers treated for drug resistant TB in pregnancy. Critical case history assessment is important to identify risks and guide clinical practice.
METHODS: In a cohort of pregnant women with multidrug or rifampicin resistant (MDR/RR)-TB enrolled between 1 January 2013 and 31 December 2022, we followed mother-infant pairs until the infant was 12 months old. We performed critical case history assessments to explore potential mechanisms of Mycobacterium tuberculosis transmission to the infant, and to describe the clinical presentation and disease trajectories observed in infants diagnosed with TB.
FINDINGS: Among 101 mother-infant pairs, 23 (23%) included infants diagnosed with TB disease; 16 were clinically diagnosed and seven had microbiological confirmation (five MDR/RR-TB, two drug-susceptible TB). A positive maternal sputum culture at the time of delivery was significantly associated with infant TB risk ($p = 0.023$). Of the 12 infants diagnosed with TB in the first three months of life, seven (58%) of the mothers were culture positive at delivery; of whom four reported poor TB treatment adherence. However, health system failures, including failing to diagnose and treat maternal MDR/RR-TB, inadequate screening of newborns at birth, not providing appropriate TB preventive therapy (TPT), and M. tuberculosis transmission from non-maternal sources also contributed to TB development in infants.
INTERPRETATION: Infants born to mothers with MDR/RR-TB are at greatest risk if

maternal adherence to MDR/RR-TB treatment or antiretroviral therapy (ART) is sub-optimal. In a high TB incidence setting, infants are also at risk of non-maternal household and community transmission. Ensuring maternal TB diagnosis and appropriate treatment, together with adequate TB screening and prevention in all babies born to mothers or households with TB will minimise the risk of infant TB disease development.
FUNDING: South African Medical Research Council.

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PMID: 39290633

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39. Macrophage targeted graphene oxide nanosystem synergize antibiotic killing and host immune defense for Tuberculosis Therapy.

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Pi J(1), Chen D(2), Wang J(2), Yang E(3), Yang J(4), Liu Y(4), Yu J(4), Xia J(5), Huang X(4), Chen L(4), Ruan Y(2), Xu JF(4), Yang F(6), Shen L(7).

Author information:
(1)Research Center of Nano Technology and Application Engineering, The First Dongguan Affiliated Hospital, Dongguan Innovation Institute, Guangdong Medical University, China; Guangdong Provincial Key Laboratory of Medical Immunology and Molecular Diagnostics, School of Medical Technology, Guangdong Medical University, Dongguan, Guangdong, China. Electronic address: jiangpi@gdmu.edu.cn.
(2)Research Center of Nano Technology and Application Engineering, The First Dongguan Affiliated Hospital, Dongguan Innovation Institute, Guangdong Medical University, China.
(3)Department of Microbiology and Immunology, University of Illinois at Chicago, Chicago, IL 60612, USA; Clinic and Research Center of Tuberculosis, Shanghai Key Lab of Tuberculosis, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai, China.
(4)Research Center of Nano Technology and Application Engineering, The First Dongguan Affiliated Hospital, Dongguan Innovation Institute, Guangdong Medical University, China; Guangdong Provincial Key Laboratory of Medical Immunology and Molecular Diagnostics, School of Medical Technology, Guangdong Medical University, Dongguan, Guangdong, China.
(5)Department of Biochemistry and Molecular Biology, School of Basic Medical

Sciences, Kunming Medical University, Kunming, China.
(6)Research Center of Nano Technology and Application Engineering, The First Dongguan Affiliated Hospital, Dongguan Innovation Institute, Guangdong Medical University, China; Guangdong Provincial Key Laboratory of Medical Immunology and Molecular Diagnostics, School of Medical Technology, Guangdong Medical University, Dongguan, Guangdong, China. Electronic address: yangfen@gdmu.edu.cn.
(7)Department of Microbiology and Immunology, University of Illinois at Chicago, Chicago, IL 60612, USA. Electronic address: lshen@uic.edu.

Tuberculosis (TB), a deadly disease caused by Mycobacterium tuberculosis (Mtb) infection, remains one of the top killers among infectious diseases worldwide. How to increase targeting effects of current anti-TB chemotherapeutics and enhance anti-TB immunological responses remains a big challenge in TB and drug-resistant TB treatment. Here, mannose functionalized and polyetherimide protected graphene oxide system (GO-PEI-MAN) was designed for macrophage-targeted antibiotic (rifampicin) and autophagy inducer (carbamazepine) delivery to achieve more effective Mtb killings by combining targeted drug killing and host immunological clearance. GO-PEI-MAN system demonstrated selective uptake by in vitro macrophages and ex vivo macrophages from macaques. The endocytosed GO-PEI-MAN system would be transported into lysosomes, where the drug loaded Rif@Car@GO-PEI-MAN system would undergo accelerated drug release in acidic lysosomal conditions. Rif@Car@GO-PEI-MAN could significantly promote autophagy and apoptosis in Mtb infected macrophages, as well as induce anti-bacterial M1 polarization of Mtb infected macrophages to increase anti-bacterial IFN-γ and nitric oxide production. Collectively, Rif@Car@GO-PEI-MAN demonstrated effectively enhanced intracellular Mtb killing effects than rifampicin, carbamazepine or GO-PEI-MAN alone in Mtb infected macrophages, and could significantly reduce mycobacterial burdens in the lung of infected mice with alleviated pathology and inflammation without systemic toxicity. This macrophage targeted nanosystem synergizing increased drug killing efficiency and enhanced host immunological defense may be served as more effective therapeutics against TB and drug-resistant TB.

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

40. Pharmacokinetics and safety of TBAJ-876, a novel antimycobacterial diarylquinoline, in healthy subjects.

Antimicrob Agents Chemother. 2024 Oct 8;68(10):e0061324. doi: 10.1128/aac.00613-24. Epub 2024 Aug 28.

Lombardi A(1), Pappas F(1), Nedelman J(1), Hickman D(1), Jaw-Tsai S(2), Olugbosi M(1), Bruinenberg P(3), Beumont M(1), Sun E(1).

Author information:
(1)Global Alliance for TB Drug Development, New York, New York, USA.
(2)Sarah Jaw-Tsai Consulting Services, San Francisco, California, USA.
(3)Vast Therapeutics, Durham, North Carolina, USA.

TBAJ-876, a second-generation diarylquinoline with greater antimycobacterial activity and a potentially better safety profile compared with bedaquiline, is under development for the treatment of drug-susceptible and drug-resistant tuberculosis (TB). A phase 1, first-in-human study of TBAJ-876, comprising a single-ascending dose (SAD) part including a food effect cohort, a multiple-ascending dose (MAD) part, and a relative bioavailability part of tablets versus oral suspension, was conducted on 137 healthy adults. A drug-drug interaction study was conducted on 28 healthy adults to evaluate the effects of TBAJ-876 on a cytochrome P450 3A4 substrate (midazolam) and a P-glycoprotein substrate (digoxin). TBAJ-876 was well-tolerated at single doses up to 800 mg and multiple doses up to 200 mg for 14 days. No deaths or serious adverse events occurred. No episodes of clinically significant prolongation of the QTc interval were observed. TBAJ-876 exposures were dose proportional in the SAD and MAD studies. TBAJ-876 exhibited multicompartmental pharmacokinetics (PK) with a long terminal half-life yielding quantifiable concentrations up to the longest follow-up of 10 weeks after a single dose and resulting in accumulation with multiple dosing. In the fed state, TBAJ-876 exposures approximately doubled with the tablet formulation, whereas M3 metabolite exposures decreased by approximately 20%. The relative bioavailability of TBAJ-876 was similar between tablets and the oral suspension at 100-mg doses. With co-administration of TBAJ-876, the AUC0-inf of midazolam was unchanged and the Cmax was reduced by 14%; the AUC0-last of digoxin was increased by 51%, and the Cmax was increased by 18%. These results support further investigation of TBAJ-876 for the treatment of tuberculosis.

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

41. Characterization of novel double-reporter strains of Mycobacterium abscessus for drug discovery: a study in mScarlet.

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Bento CM(1)(2)(3), van Calster K(4), Piller T(4), Oliveira GS(1)(5), de Vooght L(4), Cappoen D(4), Cos P(4), Gomes MS(1)(5), Silva T(1)(5).

Author information:
(1)i3S-Instituto de Investigação e Inovação e Saúde, Universidade do Porto, Porto, Portugal.
(2)IBMC-Instituto de Biologia Celular e Molecular, Universidade do Porto, Porto, Portugal.
(3)Programa Doutoral em Biologia Molecular e Celular (MCBiology), Instituto de Ciências Biomédicas Abel Salazar da Universidade do Porto, Porto, Portugal.
(4)Laboratory for Microbiology, Parasitology and Hygiene (LMPH), Wilrijk, Belgium.
(5)ICBAS-Instituto de Ciências Biomédicas Abel Salazar da Universidade do Porto, Porto, Portugal.

Mycobacterium abscessus (Mab) is an emerging pathogen that poses a severe health threat, especially in people with cystic fibrosis and other chronic lung diseases. Available drugs are largely ineffective due to an exquisite intrinsic resistance, making Mab infections only comparable to multidrug-resistant tuberculosis. Current treatment is based on lengthy multidrug therapy, complicated by poor outcomes and high rates of treatment failure, recurrence, and mortality. Thus, finding new and more efficient drugs to combat this pathogen is urgent. However, drug discovery efforts targeting Mab have been limited, and traditional drug screening methods are labor-intensive, low-throughput, and do not reflect clinical effectiveness. Therefore, this work aimed to develop a new, efficient, and reliable tool for drug screening against Mab that can be used in vitro for identifying hits in a high-throughput manner and in vivo to select drug candidates for future clinical trials. We engineered two stable double-reporter strains of Mab capable of emitting strong fluorescent and luminescent signals. This is due to the expression of mScarlet protein and luciferase enzyme or the entire lux operon. Importantly, these strains maintain the same ground characteristics as the non-transformed Mab strain. We show that these new strains can be applied to various setups, from MIC determination in broth cultures and macrophage infection assays to in vivo infection (using the Galleria mellonella model). Using these strains enhances the potential for high-throughput screening of thousands of compounds in a fast and reliable way. IMPORTANCE: Mycobacterium abscessus (Mab) is currently considered an "incurable nightmare." Its intrinsic resistance, high toxicity, long duration, and low cure rates of available therapies often lead to the clinical decision not to treat. Moreover, one of the significant drawbacks of anti-Mab drug development is the

lack of correlation between in vitro susceptibility and clinical efficacy. Most drug screening assays are performed on Mab growing in liquid cultures. But being an intracellular pathogen, inducing granulomas and biofilm formation, the broth culture is far from ideal as in vitro drug-testing setup. This study presents new double-reporter Mab strains that allow direct real-time bacterial detection and quantification in a non-invasive way. These strains can be applied to an extensive range of experimental settings, far surpassing the utility of single-reporter bacteria. They can be used in all steps of the pre-clinical anti-Mab drug development pipeline, constituting a highly valuable tool to increase its success.

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PMID: 39189762 [Indexed for MEDLINE]

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

42. Clofazimine and QT prolongation in the treatment of rifampicin-resistant tuberculosis: Findings of aDSM in Taiwan.

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Lin CJ(1), Chen JH(2), Chien ST(3), Huang YW(4), Lin CB(5), Lee JJ(6), Lee CH(7), Yu MC(8), Chiang CY(9).

Author information:
(1)Tao-Yuan General Hospital, Ministry of Health and Welfare, 1492, Zhongshan Road, Taoyuan District, Taoyuan City, 330, Taiwan.
(2)Office of Data Science, Taipei Medical University, 301 Yuantong Road, Zhonghe District, New Taipei City, 235, Taiwan.
(3)Chest Hospital, Ministry of Health and Welfare, 864 Zhongshan Road, Rende District, Tainan City, 717, Taiwan.
(4)Chang-Hua Hospital, Ministry of Health and Welfare, 80 Zhongzheng Road, Section 2, Puxin Township, Changhua County, 513, Taiwan; Institute of Medicine, Chang Shan Medical University, 110 Jianguo North Road, Section 1, Taichung City, 402, Taiwan.
(5)Division of Chest Medicine, Department of Internal Medicine, Tzu Chi General Hospital, Tzu Chi University, 707 Chung-Yang Road, Section 3, Hualien, 970, Taiwan; School of Medicine, Tzu Chi University, 701 Zhongyang Road, Section 3, Hualien, 970, Taiwan.
(6)Division of Chest Medicine, Department of Internal Medicine, Tzu Chi General Hospital, Tzu Chi University, 707 Chung-Yang Road, Section 3, Hualien, 970, Taiwan.

(7)Division of Pulmonary Medicine, Department of Internal Medicine, Wan Fang Hospital, Taipei Medical University, 111 Hsin-Long Road, Section 3, Taipei City, 116, Taiwan; Department of Internal Medicine, School of Medicine, College of Medicine, Taipei Medical University, 250 Wuxing Street, Xinyi District, Taipei City, 110, Taiwan.
(8)Division of Pulmonary Medicine, Department of Internal Medicine, Wan Fang Hospital, Taipei Medical University, 111 Hsin-Long Road, Section 3, Taipei City, 116, Taiwan; School of Respiratory Therapy, College of Medicine, Taipei Medical University, 250 Wuxing Street, Xinyi District, Taipei City, 110, Taiwan.
(9)Division of Pulmonary Medicine, Department of Internal Medicine, Wan Fang Hospital, Taipei Medical University, 111 Hsin-Long Road, Section 3, Taipei City, 116, Taiwan; Department of Internal Medicine, School of Medicine, College of Medicine, Taipei Medical University, 250 Wuxing Street, Xinyi District, Taipei City, 110, Taiwan; International Union Against Tuberculosis and Lung Disease, 2 Rue Jean Lantier, 75001, Paris, France. Electronic address: cychiang@theunion.org.

BACKGROUND: Bedaquiline, delamanid and fluoroquinolones are associated with increased QTcF. Whether clofazimine is associated with QTcF prolongation is less clear.
METHODS: All patients with rifampicin-resistant TB enrolled between May 2017 and Dec 2019 were included. ECGs were performed at baseline, month 1, month 3 and month 6 for patients treated with conventional regimens, and at additional timepoint for patients treated with bedaquiline, delamanid and short regimen. We estimated the maximum increase of QTcF and constructed cox proportional hazards models to assess factors associated with QTcF≥501ms.
RESULTS: Among 321 patients, 59 (18.4%) patients had QTcF≥501ms during a mean follow-up of 242 days (median 189, range 4-1091). The median maximum increase of QTcF was 43.4 ms (IQR 31.3-65.9) in patients treated with clofazimine. Treatment with clofazimine was significantly associated with QTcF≥501ms as compared to without clofazimine (adjusted hazards ratio (adjHR) 4.35, 95% confidence interval (CI) 2.01-9.44). Among patients not treated with bedaquiline and delamanid, those treated with clofazimine and a fluoroquinolone (adjHR 3.43, 95% CI 1.61-7.34) and those treated with clofazimine and high dose moxifloxacin (adjHR 6.54, 95% CI 2.43-17.60) had a significantly higher risk of QTcF≥501ms as compared to those treated with a fluoroquinolone without other QTcF prolonging agents. Four (1.6%) patients had documented ventricular tachycardia, in which one was Torsade de pointes. One patient was found to have sudden death during hospitalization.
CONCLUSIONS: Clofazimine was significantly associated with an increased risk of QTcF prolongation. QTcF≥501ms was potentially associated with fatal event and needed to be managed cautiously.

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PMID: 39160114 [Indexed for MEDLINE]

Conflict of interest statement: Declaration of competing interest None declared.

43. Transmission dynamics of tuberculosis in a high-burden area of China: An 8-year population-based study using whole genome sequencing.

Int J Infect Dis. 2024 Oct;147:107210. doi: 10.1016/j.ijid.2024.107210. Epub 2024 Aug 14.

He W(1), Tan Y(2), Song Z(3), Liu B(2), Xia H(4), Zheng H(5), Liu D(3), Liu C(6), He P(3), Wang Y(7), Zhao Z(8), Ou X(4), Wang S(4), Guo J(2), Zhao Y(9).

Author information:
(1)Department of Clinical Laboratory, Beijing Tongren Hospital, Capital Medical University, Beijing, China.
(2)Hunan Provincial Chest Hospital, Tuberculosis Control Institution of Hunan Province, Changsha, Hunan, China.
(3)National Institute for Communicable Disease Control and Prevention, Chinese Center for Disease Control and Prevention, Beijing, China.
(4)National Tuberculosis Reference Laboratory, Chinese Center for Disease Control and Prevention, Beijing, China.
(5)Beijing Pediatric Research Institute, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing, China.
(6)Department of Animal Science and Technology, Beijing University of Agriculture, Beijing, China.
(7)Beijing Centers for Disease Control and Prevention, Beijing, China.
(8)School of Basic Medical Sciences, Tianjin Medical University, Tianjin, China.
(9)National Tuberculosis Reference Laboratory, Chinese Center for Disease Control and Prevention, Beijing, China. Electronic address: zhaoyl@chinacdc.cn.

OBJECTIVES: This study investigated the transmission patterns of tuberculosis (TB) and its associated risk factors in Hunan province to inform the development of prevention and control strategies in the region.
METHODS: An 8-year retrospective population-based genomic epidemiological study was conducted. Genomic clusters were defined using distance thresholds of 12-single-nucletide-polymorphisms. Risk factors associated with TB transmission were analyzed using logistic regression model. Kernel Density analysis was used to locate hotspots where transmission occurred.
RESULTS: Among 2649 TB cases included in this study, 275 clusters were identified, with an overall clustering rate of 24.7% (654/2649). Nearly 95% (620/654) of clustered strains were isolated from the same county. Of the 275

clusters, 23 (8.4%, 23/275) had differences in drug-resistant profiles, with FQs resistance mutations occurring most frequently (52.2%, 12/23). Multivariate analysis identified male TB patients, those aged 30-60 years, ethnic minorities, nonfarmers, retreated TB patients, and individuals infected with MDR/RR-TB as independent risk factors for TB transmission ($P < 0.05$). Kernel density analysis showed that among the 5 drug-resistant surveillance sites, Leiyang had the highest clustering rate, followed by Yongshun, Qidong, Hecheng, and Taojiang. CONCLUSION: Recent transmission in the region is predominantly occurring within counties. The risk factors related to TB transmission and the hotspots where transmission occurs can provide a scientific basis for the formulation of targeted TB prevention and control strategies.

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PMID: 39151786 [Indexed for MEDLINE]

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44. Increased risk of adverse drug reactions by higher linezolid dose per weight in multidrug-resistant tuberculosis.

Int J Antimicrob Agents. 2024 Oct;64(4):107302. doi: 10.1016/j.ijantimicag.2024.107302. Epub 2024 Aug 13.

Kuhlin J(1), Davies Forsman L(2), Osman A(3), Skagerberg M(4), Jonsson J(5), Groenheit R(6), Mansjö M(6), Werngren J(6), Alffenaar JW(7), Schön T(8), Bruchfeld J(2).

Author information:
(1)Department of Medicine, Division of Infectious Diseases, Karolinska Institutet, Solna, Sweden; Department of Infectious Diseases, Karolinska University Hospital, Stockholm, Sweden. Electronic address: Johanna.kuhlin@ki.se.
(2)Department of Medicine, Division of Infectious Diseases, Karolinska Institutet, Solna, Sweden; Department of Infectious Diseases, Karolinska University Hospital, Stockholm, Sweden.
(3)Department of Medicine, Division of Infectious Diseases, Karolinska Institutet, Solna, Sweden.
(4)Department of Infectious Diseases, Karolinska University Hospital, Stockholm, Sweden.

(5)Department of Public Health Analysis and Data Management, Public Health Agency of Sweden, Stockholm, Sweden.
(6)Department of Microbiology, Public Health Agency of Sweden, Stockholm, Sweden.
(7)Faculty of Medicine and Health, University of Sydney, Sydney, NSW, Australia; Research and Education Network, Westmead Hospital, Sydney, NSW, Australia; The University of Sydney Institute for Infectious Diseases (Sydney ID), The University of Sydney, Sydney, NSW, Australia.
(8)Department of Biomedical and Clinical Sciences, Linköping University, Linköping, Sweden; Department of Microbiology, Linköping University Hospital, Linköping, Sweden; Department of Clinical Microbiology and Infectious Diseases, Kalmar County Hospital, Kalmar, Sweden.

OBJECTIVES: Linezolid treatment has a high risk of toxicity and adverse drug reactions (ADR) are frequent. Few studies have investigated risk factors of major ADRs separately, therefore, we aimed to evaluate major ADRs including peripheral neuropathy in relation to risk factors and drug concentration levels of linezolid in a high-resource setting for multidrug-resistant tuberculosis (MDR-TB).
METHODS: We conducted a retrospective cohort study including participants treated with a linezolid-containing MDR-TB regimen in Sweden 1992-2018. Data was collected from medical records. ADRs were classified according to Common Terminology Criteria for Adverse Events (version 5.0).
RESULTS: Of all participants (n = 132), 43.2% were female and the median age 28 y. The median linezolid treatment was 6.5 months (IQR 3.0-12.7) with a median daily dose of 9.6 mg/kg/d. Any ADR was seen in 58.3% (n = 77) of participants, with 35.6% having peripheral neuropathy (n = 47), 27.3% anaemia (n = 36), 22.0% leukopenia (n = 36) while 6.1% (n = 8) had optic neuritis. The median time for peripheral neuropathy was 3.6 months (IQR 2.1-5.9) and 8.3 months (6.2-10.7) for optic neuritis. A >2.0 mg/L trough concentration (n = 40) was associated with anaemia (P = 0.0038) and thrombocytopenia (P = 0.009) but not with peripheral neuropathy. In multivariable analysis, a dose ≥12 mg/kg/d was associated with time to peripheral neuropathy (HR 2.89, 95% CI 1.08-7.74, P = 0.035), anaemia (HR 6.62, 95% CI 2.22-19.8, P = 0.001) and leukopenia (HR 5.23, 95% CI 1.48-18.5, P = 0.010).
CONCLUSIONS: Linezolid ADRs were frequent in a high-resource setting. Structured, regular follow-up for ADRs and adjusting dosing according to body weight followed-up by monitoring of drug concentrations early may reduce toxicity.

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PMID: 39146999 [Indexed for MEDLINE]

Conflict of interest statement: Declaration of competing interests JJ is heading the Swedish national advisory board on MDR-TB and other difficult to treat cases and JB, LDF and TS are also members of the advisory board. JW is the scientific secretary in the EUCAST steering committee on antimycobacterial susceptibility testing, which is an unpaid position. JWA has been giving lectures on an infectious diseases conference on therapeutic drug monitoring for linezolid and received an educational fee from Pfizer. JB received a payment fee for lectures on Post-COVID by Astra Zeneca and Novartis. JK, AO, MS, MM, and RG have no conflict of interest to declare.

45. Investigating the treatment shortening potential of a combination of bedaquiline, delamanid and moxifloxacin with and without sutezolid, in a murine tuberculosis model with confirmed drug exposures.

J Antimicrob Chemother. 2024 Oct 1;79(10):2607-2610. doi: 10.1093/jac/dkae266.

Walter K(1)(2), Te Brake LHM(3), Lemm AK(1), Hoelscher M(4)(5)(6)(7), Svensson EM(3)(8), Hölscher C(1)(2), Heinrich N(4)(5)(6).

Author information:
(1)Division of Infection Immunology, Research Center Borstel, Leibniz Lung Center, Borstel, Germany.
(2)German Center for Infection Research, Partner Site Hamburg-Lübeck-Borstel-Riems, Borstel, Germany.
(3)Department of Pharmacy, Radboud Institute of Health Sciences, Radboud University Medical Center, Nijmegen, The Netherlands.
(4)Institute of Infectious Diseases and Tropical Medicine, University Hospital, LMU Munich, Munich, Germany.
(5)German Center for Infection Research, Partner Site Munich, Munich, Germany.
(6)Fraunhofer Institute ITMP, Immunology, Infection and Pandemic Research, Munich, Germany.
(7)Unit Global Health, Helmholtz Zentrum Munich, German Research Center for Environmental Health (HMGU), Neuherberg, Germany.
(8)Department of Pharmacy, Uppsala University, Uppsala, Sweden.

BACKGROUND: New and shorter regimens against multi-drug resistant tuberculosis (TB) remain urgently needed. To inform treatment duration in clinical trials, this study aimed to identify human pharmacokinetic equivalent doses, antimycobacterial and sterilizing activity of a novel regimen, containing bedaquiline, delamanid, moxifloxacin and sutezolid (BDMU), in the standard mouse model (BALB/c) of Mycobacterium tuberculosis (Mtb) infection.
METHODS: Treatment of mice with B25D0.6M200U200, B25D0.6M200, B25D0.6M200(U2003)

or H10R10Z150E100 (isoniazid, rifampicin, pyrazinamide, ethambutol, HRZE), started 3 weeks after Mtb infection. Bactericidal activity was assessed after 1, 2, 3 and 4 months of treatment and relapse rates were assessed 3 months after completing treatment durations of 2, 3 and 4 months.
RESULTS: B25D0.6M200U200 generated human equivalent exposures in uninfected BALB/c mice. After 1 month of treatment, a higher bactericidal activity was observed for the B25D0.6M200U200 and the B25D0.6M200 regimen compared to the standard H10R10Z150E100 regimen. Furthermore, 3 months of therapy with both BDM-based regimens resulted in negative lung cultures, whereas all H10R10Z150E100 treated mice were still culture positive. After 3 months of therapy 7% and 13% of mice relapsed receiving B25D0.6M200U200 and B25D0.6M200, respectively, compared to 40% for H10R10Z150E100 treatment showing an increased sterilizing activity of both BDM-based regimens.
CONCLUSIONS: BDM-based regimens, with and without sutezolid, have a higher efficacy than the HRZE regimen in the BALB/c model of TB, with some improvement by adding sutezolid. By translating these results to TB patients, this novel BDMU regimen should be able to reduce treatment duration by 25% compared to HRZE therapy.

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PMCID: PMC11441997
PMID: 39110473 [Indexed for MEDLINE]

46. A pharmacometric multistate model for predicting long-term treatment outcomes of patients with pulmonary TB.

J Antimicrob Chemother. 2024 Oct 1;79(10):2561-2569. doi: 10.1093/jac/dkae256.

Lin YJ(1), Zou Y(1), Karlsson MO(1), Svensson EM(1)(2).

Author information:
(1)Department of Pharmacy, Uppsala University, Uppsala, Sweden.
(2)Department of Pharmacy, Radboud University Medical Center, Nijmegen, The Netherlands.

BACKGROUND: Studying long-term treatment outcomes of TB is time-consuming and impractical. Early and reliable biomarkers reflecting treatment response and capable of predicting long-term outcomes are urgently needed.
OBJECTIVES: To develop a pharmacometric multistate model to evaluate the link between potential predictors and long-term outcomes.
METHODS: Data were obtained from two Phase II clinical trials (TMC207-C208 and

TMC207-C209) with bedaquiline on top of a multidrug background regimen. Patients were typically followed throughout a 24 week investigational treatment period plus a 96 week follow-up period. A five-state multistate model (active TB, converted, recurrent TB, dropout, and death) was developed to describe observed transitions. Evaluated predictors included patient characteristics, baseline TB disease severity and on-treatment biomarkers.
RESULTS: A fast bacterial clearance in the first 2 weeks and low TB bacterial burden at baseline increased probability to achieve conversion, whereas patients with XDR-TB were less likely to reach conversion. Higher estimated mycobacterial load at the end of 24 week treatment increased the probability of recurrence. At 120 weeks, the model predicted 55% (95% prediction interval, 50%-60%), 6.5% (4.2%-9.0%) and 7.5% (5.2%-10%) of patients in converted, recurrent TB and death states, respectively. Simulations predicted a substantial increase of recurrence after 24 weeks in patients with slow bacterial clearance regardless of baseline bacterial burden.
CONCLUSIONS: The developed multistate model successfully described TB treatment outcomes. The multistate modelling framework enables prediction of several outcomes simultaneously, and allows mechanistically sound investigation of novel promising predictors. This may help support future biomarker evaluation, clinical trial design and analysis.

DOI: 10.1093/jac/dkae256
PMCID: PMC11441995
PMID: 39087258 [Indexed for MEDLINE]

47. Readability of Patient-Facing Information of Antibiotics Used in the WHO Short 6-Month and 9-Month All Oral Treatment for Drug-Resistant Tuberculosis.

Lung. 2024 Oct;202(5):741-751. doi: 10.1007/s00408-024-00732-z. Epub 2024 Jul 26.

Moore JE(1)(2), Millar BC(3)(4).

Author information:
(1)School of Biomedical Sciences, Ulster University, Cromore Road, Coleraine, Northern Ireland, BT52 1SA, UK. je.moore1@ulster.ac.uk.
(2)Laboratory for Disinfection and Pathogen Elimination Studies, Northern Ireland Public Health Laboratory, Belfast City Hospital, Lisburn Road, Belfast, Northern Ireland, BT9 7AD, UK. je.moore1@ulster.ac.uk.
(3)School of Biomedical Sciences, Ulster University, Cromore Road, Coleraine, Northern Ireland, BT52 1SA, UK.

(4)Laboratory for Disinfection and Pathogen Elimination Studies, Northern Ireland Public Health Laboratory, Belfast City Hospital, Lisburn Road, Belfast, Northern Ireland, BT9 7AD, UK.

OBJECTIVES: Readability of patient-facing information of oral antibiotics detailed in the WHO all oral short (6 months, 9 months) has not been described to date. The aim of this study was therefore to examine (i) how readable patient-facing TB antibiotic information is compared to readability reference standards and (ii) if there are differences in readability between high-incidence countries versus low-incidence countries.
METHODS: Ten antibiotics, including bedaquiline, clofazimine, ethambutol, ethionamide, isoniazid, levofloxacin, linezolid, moxifloxacin, pretomanid, pyrazinamide, were investigated. TB antibiotic information sources were examined, consisting of 85 Patient Information Leaflets (PILs) and 40 antibiotic web resouces. Of these 85 PILs, 72 were taken from the National Medicines Regulator from six countries (3 TB high-incidence [Rwanda, Malaysia, South Africa] + 3 TB low-incidence [UK, Ireland, Malta] countries). Readability data was grouped into three categories, including (i) high TB-incidence countries (n = 33 information sources), (ii) low TB-incidence countries (n = 39 information sources) and (iii) web information (n = 53). Readability was calculated using Readable software, to obtain four readability scores [(i) Flesch Reading Ease (FRE), (ii) Flesch-Kincaid Grade Level (FKGL), (iii) Gunning Fog Index and (iv) SMOG Index], as well as two text metrics [words/sentence, syllables/word].
RESULTS: Mean readability scores of patient-facing TB antibiotic information for FRE and FKGL, were 47.4 ± 12.6 (sd) (target ≥ 60) and 9.2 ± 2.0 (target ≤ 8.0), respectively. There was no significant difference in readability between low incidence countries and web resources, but there was significantly poorer readability associated with PILs from high incidence countries versus low incidence countries (FRE; p = 0.0056: FKGL; p = 0.0095).
CONCLUSIONS: Readability of TB antibiotic PILs is poor. Improving readability of PILs should be an important objective when preparing patient-facing written materials, thereby improving patient health/treatment literacy.

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PMID: 39060416 [Indexed for MEDLINE]

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

48. Pharmacovigilance in Pregnancy Studies, Exposures and Outcomes Ascertainment, and Findings from Low- and Middle-Income Countries: A Scoping Review.

Drug Saf. 2024 Oct;47(10):957-990. doi: 10.1007/s40264-024-01445-1. Epub 2024 Jun 21.

Shafi J(#)(1), Virk MK(#)(1), Kalk E(2), Carlucci JG(3), Chepkemoi A(4), Bernard C(3), McHenry MS(3), Were E(4), Humphrey J(3), Davies MA(2), Mehta UC(2), Patel RC(5)(6).

Author information:
(1)University of Washington, Seattle, WA, USA.
(2)Centre for Infectious Disease Epidemiology & Research, School of Public Health, University of Cape Town, Cape Town, South Africa.
(3)Indiana University, Indianapolis, IN, USA.
(4)Moi University, Eldoret, Kenya.
(5)University of Washington, Seattle, WA, USA. renapatel@uabmc.edu.
(6)University of Alabama at Birmingham, Birmingham, AL, USA. renapatel@uabmc.edu.
(#)Contributed equally

INTRODUCTION: Pharmacovigilance (PV), or the ongoing safety monitoring after a medication has been licensed, plays a crucial role in pregnancy, as clinical trials often exclude pregnant people. It is important to understand how pregnancy PV projects operate in low- and middle-income countries (LMICs), where there is a disproportionate lack of PV data yet a high burden of adverse pregnancy outcomes. We conducted a scoping review to assess how exposures and outcomes were measured in recently published pregnancy PV projects in LMICs.
METHODS: We utilized a search string, secondary review, and team knowledge to review publications focusing on therapeutic or vaccine exposures among pregnant people in LMICs. We screened abstracts for relevance before conducting a full text review, and documented measurements of exposures and outcomes (categorized as maternal, birth, or neonatal/infant) among other factors, including study topic, setting, and design, comparator groups, and funding sources.
RESULTS: We identified 31 PV publications spanning at least 24 LMICs, all focusing on therapeutics or vaccines for infectious diseases, including HIV (n = 17), tuberculosis (TB; n = 9), malaria (n = 7), pertussis, tetanus, and diphtheria (n = 1), and influenza (n = 3). As for outcomes, n = 15, n = 31, and n = 20 of the publications covered maternal, birth, and neonatal/infant outcomes, respectively. Among HIV-specific publications, the primary exposure-outcome relationship of focus was exposure to maternal antiretroviral therapy and adverse outcomes. For TB-specific publications, the main exposures of interest were second-line drug-resistant TB and isoniazid-based prevention

therapeutics for pregnant people living with HIV. For malaria-specific publications, the primary exposure-outcome relationship of interest was antimalarial medication exposure during pregnancy and adverse outcomes. Among vaccine-focused publications, the exposure was assessed during a specific time during pregnancy, with an overall interest in vaccine safety and/or efficacy. The study settings were frequently from Africa, designs varied from cohort or cross-sectional studies to clinical trials, and funding sources were largely from high-income countries.
CONCLUSION: The published pregnancy PV projects were largely centered in Africa and concerned with infectious diseases. This may reflect the disease burden in LMICs but also funding priorities from high-income countries. As the prevalence of non-communicable diseases increases in LMICs, PV projects will have to broaden their scope. Birth and neonatal/infant outcomes were most reported, with fewer reporting on maternal outcomes and none on longer-term child outcomes; additionally, heterogeneity existed in definitions and ascertainment of specific measures. Notably, almost all projects covered a single therapeutic exposure, missing an opportunity to leverage their projects to cover additional exposures, add scientific rigor, create uniformity across health services, and bolster existing health systems. For many publications, the timing of exposure, specifically by trimester, was crucial to maternal and neonatal safety. While currently published pregnancy PV literature offer insights into the PV landscape in LMICs, further work is needed to standardize definitions and measurements, integrate PV projects across health services, and establish longer-term monitoring.

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49. Effectiveness and safety of modified fully oral 9-month treatment regimens for rifampicin-resistant tuberculosis: a prospective cohort study.

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Korotych O(1), Achar J(2), Gurbanova E(3), Hovhannesyan A(4), Lomtadze N(5), Ciobanu A(4), Skrahina A(6), Dravniece G(7), Kuksa L(8), Rich M(9), Khachatryan N(10), Germanovych M(11), Kadyrov A(12), Terleieva I(13), Akhundova I(14), Adenov M(15), Durdyeva M(16), Kiria N(17), Parpieva N(18), Yatskevich N(6),

Jumayev R(19), Nurov R(20), Diktanas S(21), Vilc V(22), Migliori GB(23), Yedilbayev A(4).

Author information:
(1)Division of Communicable Diseases, Environment, and Health, WHO Regional Office for Europe, Copenhagen, Denmark. Electronic address: korotycho@who.int.
(2)Department of Global Public Health, Karolinska Institutet, Stockholm, Sweden; Department for Science and Innovation-National Research Fund Centre of Excellence for Biomedical Tuberculosis Research, 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.
(3)Lung Clinic, University of Tartu, Tartu, Estonia.
(4)Division of Communicable Diseases, Environment, and Health, WHO Regional Office for Europe, Copenhagen, Denmark.
(5)National Center for Tuberculosis and Lung Diseases, Tbilisi, Georgia; The University of Georgia, Tbilisi, Georgia.
(6)The Republican Scientific and Practical Center for Pulmonology and Tuberculosis, Minsk, Belarus.
(7)PATH, Kyiv, Ukraine.
(8)TB and Lung Disease Clinic, Riga East University Hospital, Riga, Latvia.
(9)Partners In Health, Boston, MA, United States of America.
(10)National Center of Pulmonology of the Ministry of Health of Armenia, Abovyan, Armenia.
(11)Division of Communicable Diseases, Environment, and Health, WHO Regional Office for Europe, Copenhagen, Denmark; State Institution "Public Health Center of the Ministry of Health of Ukraine", Kyiv, Ukraine.
(12)National Center of Phthisiology, Ministry of Health of Kyrgyzstan, Bishkek, Kyrgyzstan.
(13)State Institution "Public Health Center of the Ministry of Health of Ukraine", Kyiv, Ukraine.
(14)Scientific Research Institute of Lung Diseases, Baku, Azerbaijan.
(15)National Scientific Center of Phthisiopulmonology of the Republic of Kazakhstan, Almaty, Kazakhstan.
(16)Turkmen State Medical University, Ashgabat, Turkmenistan.
(17)National Center for Tuberculosis and Lung Diseases, Tbilisi, Georgia.
(18)Republican Specialized Scientific-Practical Medical Center of Phthisiology And Pulmonology, Ministry of Health, Tashkent, Uzbekistan.
(19)National Tuberculosis Treatment and Prevention Center, Directorate of Communicable Diseases, Ashgabat, Turkmenistan.
(20)Republican Center for Protection of the Population from Tuberculosis, Ministry of Health and Social Protection of the Population, Dushanbe, Tajikistan.
(21)Republican Klaipeda Hospital, Tuberculosis Branch, Klaipeda, Lithuania.

(22)The Institute of Phthisiopneumology, Chisinau, Republic of Moldova.
(23)Istituti Clinici Scientifici Maugeri, Istituto di Ricovero e Cura a Carattere Scientifico, Tradate, Italy.

BACKGROUND: In 2020, WHO guidelines prioritised the use of a standard fully oral short treatment regimen (STR) consisting of bedaquiline, levofloxacin or moxifloxacin, ethionamide, ethambutol, high-dose isoniazid, pyrazinamide, and clofazimine for the management of rifampicin-resistant tuberculosis. A high prevalence of resistance to constituent drugs precluded its widespread use by countries in the WHO European region. We evaluated three 9-month fully oral modified STRs (mSTRs) in which ethionamide, ethambutol, isoniazid, and pyrazinamide were replaced by linezolid, cycloserine, or delamanid (or a combination).
METHODS: This multicountry, prospective, single-arm, cohort study examined the effectiveness and safety of mSTRs for fluoroquinolone-susceptible, rifampicin-resistant pulmonary tuberculosis in 13 countries in the WHO European region during 2020-23. We enrolled adults and children of all ages with bacteriologically confirmed rifampicin-resistant, fluoroquinolone-susceptible pulmonary tuberculosis, and children (aged 0-18 years) with clinically diagnosed disease and a confirmed contact with rifampicin-resistant, fluoroquinolone-susceptible tuberculosis. Participants aged 6 years or older received one of two regimens: bedaquiline, linezolid, levofloxacin, clofazimine, and cycloserine; or bedaquiline, linezolid, levofloxacin, clofazimine, and delamanid. Children younger than 6 years received delamanid, linezolid, levofloxacin, and clofazimine. Participants were followed up for 12 months after successful treatment completion to detect recurrence and death. The primary outcome was the cumulative probability of not having an unsuccessful study outcome (defined as treatment failure, on-treatment loss to follow-up, death, or recurrence) before 22 months of study follow-up. The primary safety outcome was the incidence of each adverse event of interest (peripheral neuropathy, optic neuritis, myelosuppression, hepatitis, prolonged QT interval, hypokalaemia, and acute kidney injury) of grade 3 or higher severity during the treatment course.
FINDINGS: Between Aug 28, 2020 and May 26, 2021, 7272 patients were screened and 2636 were included in the treatment cohort. 1966 (74·6%) were male, 670 (25·4%) were female, and median age was 43 years (IQR 33-53). Treatment success was recorded for 2181 (82·7%) participants. The cumulative probability of not having an unsuccessful study outcome 22 months after treatment initiation was 79% (95% CI 78-81). Increasing age (adjusted hazard ratio 2·61 [95% CI 1·70-4·04] for people aged >64 years vs 35-44 years), HIV-positive status (1·53 [1·16-2·01]), presence of bilateral cavities (1·68 [1·29-2·19]), smoking history (1·34 [1·05-1·71]), baseline anaemia (1·46 [1·15-1·86]), unemployment (1·37 [1·04-1·80]), elevated baseline liver enzymes (1·40 [1·13-1·73]), and excessive alcohol use (1·47 [1·14-1·89]) were positively associated with unsuccessful study outcomes. In the safety cohort of 2813 participants who received at least

one dose, 301 adverse events of interest were recorded in 252 (9·0%) participants with the most frequent being myelosuppression (139 [4·9%] participants, 157 [52·2%] events).
INTERPRETATION: The high treatment success and good safety results indicate considerable potential for the use of mSTRs in programmatic conditions, especially for individuals not eligible for the current WHO-recommended 6-month regimen and in settings with a need for alternative options.
FUNDING: The Global Fund to Fight AIDS, Tuberculosis and Malaria; United States Agency for International Development; Government of Germany; and WHO.
TRANSLATION: For the Russian translation of the abstract see Supplementary Materials section.

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

50. Tuberculosis Disease Among Nonimmigrant Visa Holders Reported to US Quarantine Stations, January 2011-June 2016.

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Vonnahme LA(1), Shaw KM(1), Gulati RK(1), Hollberg MR(1), Posey DL(1), Regan JJ(2).

Author information:
(1)Division of Global Migration and Quarantine, Centers for Disease Control and Prevention, Atlanta, GA, USA.
(2)Division of Global Migration and Quarantine, Centers for Disease Control and Prevention, Atlanta, GA, USA. jregan@cdc.gov.

US-bound immigrants and refugees undergo a mandatory overseas medical examination that includes tuberculosis screening; this exam is not routinely

required for temporary visitors applying for non-immigrant visas (NIV) to visit, work, or study in the United States. US health departments and foreign ministries of health report tuberculosis cases in travelers to Centers for Disease Control and Prevention Quarantine Stations. We reviewed cases reported to this passive surveillance system from January 2011 to June 2016. Of 1252 cases of tuberculosis in travelers reported to CDC, 114 occurred in travelers with a long-term NIV. Of these, 83 (73%) were infectious; 18 (16%) with multidrug-resistant tuberculosis (MDR TB) and one with extensively drug-resistant tuberculosis (XDR TB). We found evidence that NIV holders are diagnosed with tuberculosis disease in the United States. Given that long-term NIV holders were over-represented in this data set, despite the small proportion (4%) of overall non-immigrant admissions they represent, expanding the US overseas migration health screening program to this population might be an efficient intervention to further reduce tuberculosis in the United States.

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PMID: 38834868 [Indexed for MEDLINE]

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51. Safety and Effectiveness of 3 Novel All-Oral Shortened Regimens for Rifampicin- or Multidrug-Resistant Tuberculosis in Kazakhstan.

Clin Infect Dis. 2024 Oct 15;79(4):1046-1053. doi: 10.1093/cid/ciae305.

Rashitov M(1), Franke MF(2)(3), Trevisi L(2), Bekbolatova G(4), Shalimova J(5), Eshmetov G(6), Bektasov S(7), LaHood A(2)(3), Arlyapova N(8), Osso E(2), Yedilbayev A(9), Korotych O(9), Ciobanu A(9), Skrahina A(10), Mitnick CD(2)(8)(11), Seung KJ(8)(11), Algozhin Y(1), Rich ML(8)(11).

Author information:
(1)Partners In Health Kazakhstan, Almaty, Kazakhstan.
(2)Department of Global Health and Social Medicine, Harvard Medical School, Boston, Massachusetts, USA.
(3)Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA.
(4)Atyrau Regional Center of Phthisiopulmonology, Atreyu, Kazakhstan.

(5)Karaganda Regional Center of Phthisiopulmonology, Karaganda, Kazakhstan.
(6)Turkistan Regional Center of Phthisiopulmonology, Turkistan, Kazakhstan.
(7)National Scientific Center of Phthisiopulmonology, Almaty, Kazakhstan.
(8)Partners In Health, Boston, Massachusetts, USA.
(9)World Health Organization, Regional Office for Europe, Copenhagen, Denmark.
(10)The Republican Scientific and Practical Centre for Pulmonology and Tuberculosis, Minsk, Belarus.
(11)Division of Global Health Equity, Brigham and Women's Hospital, Boston, Massachusetts, USA.

BACKGROUND: In 2019, the World Health Organization called for operational research on all-oral shortened regimens for multidrug- and rifampicin-resistant tuberculosis (MDR/RR-TB). We report safety and effectiveness of three 9-month all-oral regimens containing bedaquiline (Bdq), linezolid (Lzd), and levofloxacin (Lfx) and reinforced with cycloserine (Cs) and clofazimine (Cfz), delamanid (Dlm) and pyrazinamide (Z), or Dlm and Cfz.
METHODS: We conducted a prospective cohort study of patients initiating treatment for pulmonary MDR/RR-TB under operational research conditions at public health facilities in Kazakhstan. Participants were screened monthly for adverse events. Participants with baseline resistance were excluded from the study and treated with a longer regimen. We analyzed clinically relevant adverse events of special interest in all participants and sputum culture conversion and end-of-treatment outcomes among individuals who were not excluded.
RESULTS: Of 510 participants, 41% were women, the median age was 37 years (25th-75th percentile: 28-49), 18% had a body mass index <18.5 kg/m2, and 51% had cavitary disease. A total of 399 (78%) initiated Bdq-Lzd-Lfx-Cs-Cfz, 83 (16%) started Bdq-Lzd-Lfx-Dlm-Z, and 28 (5%) initiated Bdq-Lzd-Lfx-Dlm-Cfz. Fifty-eight individuals (11%) were excluded from the study, most commonly due to identification of baseline drug resistance (n = 52; 90%). Among the remaining 452 participants, treatment success frequencies were 92% (95% CI: 89-95%), 89% (95% CI: 80-94%), and 100% (95% CI: 86-100%) for regimens with Cs/Cfz, Dlm/Z, and Dlm/Cfz, respectively. Clinically relevant adverse events of special interest were uncommon.
CONCLUSIONS: All regimens demonstrated excellent safety and effectiveness, expanding the potential treatment options for patients, providers, and programs.

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reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

52. Targeted next-generation sequencing to diagnose drug-resistant tuberculosis: a systematic review and meta-analysis.

Lancet Infect Dis. 2024 Oct;24(10):1162-1176. doi: 10.1016/S1473-3099(24)00263-9. Epub 2024 May 22.

Schwab TC(1), Perrig L(1), Göller PC(1), Guebely De la Hoz FF(1), Lahousse AP(1), Minder B(2), Günther G(3), Efthimiou O(4), Omar SV(5), Egger M(6), Fenner L(7).

Author information:
(1)Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland.
(2)Public Health and Primary Care Library, University Library of Bern, University of Bern, Bern, Switzerland.
(3)Department of Pulmonology and Allergology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland; Department of Medical Science, Faculty of Health Sciences, University of Namibia, Windhoek, Namibia.
(4)Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland; Institute of Primary Health Care (BIHAM), University of Bern, Bern, Switzerland.
(5)Centre for Tuberculosis, National & WHO Supranational TB Reference Laboratory, National Institute for Communicable Diseases, a division of the National Health Laboratory Services, Johannesburg, South Africa.
(6)Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland; Centre for Infectious Disease Epidemiology & Research, School of Public Health & Family Medicine, University of Cape Town, Cape Town, South Africa; Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK.
(7)Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland. Electronic address: lukas.fenner@unibe.ch.

BACKGROUND: Targeted next-generation sequencing (NGS) can rapidly and simultaneously detect mutations associated with resistance to tuberculosis drugs across multiple gene targets. The use of targeted NGS to diagnose drug-resistant tuberculosis, as described in publicly available data, has not been comprehensively reviewed. We aimed to identify targeted NGS assays that diagnose drug-resistant tuberculosis, determine how widely this technology has been used, and assess the diagnostic accuracy of these assays.
METHODS: In this systematic review and meta-analysis, we searched MEDLINE,

Embase, Cochrane Library, Web of Science Core Collection, Global Index Medicus, Google Scholar, ClinicalTrials.gov, and the WHO International Clinical Trials Registry Platform for published and unpublished reports on targeted NGS for drug-resistant tuberculosis from Jan 1, 2005, to Oct 14, 2022, with updates to our search in Embase and Google Scholar until Feb 13, 2024. Studies eligible for the systematic review described targeted NGS approaches to predict drug resistance in Mycobacterium tuberculosis infections using primary samples, reference strain collections, or cultured isolates from individuals with presumed or confirmed tuberculosis. Our search had no limitations on study type or language, although only reports in English, German, and French were screened for eligibility. For the meta-analysis, we included test accuracy studies that used any reference standard, and we assessed risk of bias using the Quality Assessment of Diagnostic Accuracy Studies-2 tool. The primary outcomes for the meta-analysis were sensitivity and specificity of targeted NGS to diagnose drug-resistant tuberculosis compared to phenotypic and genotypic drug susceptibility testing. We used a Bayesian bivariate model to generate summary receiver operating characteristic plots and diagnostic accuracy measures, overall and stratified by drug and sample type. This study is registered with PROSPERO, CRD42022368707.

FINDINGS: We identified and screened 2920 reports, of which 124 were eligible for our systematic review, including 37 review articles and 87 reports of studies collecting samples for targeted NGS. Sequencing was mainly done in the USA (14 [16%] of 87), western Europe (ten [11%]), India (ten [11%]), and China (nine [10%]). We included 24 test accuracy studies in the meta-analysis, in which 23 different tuberculosis drugs or drug groups were assessed, covering first-line drugs, injectable drugs, and fluoroquinolones and predominantly comparing targeted NGS with phenotypic drug susceptibility testing. The combined sensitivity of targeted NGS across all drugs was 94·1% (95% credible interval [CrI] 90·9-96·3) and specificity was 98·1% (97·0-98·9). Sensitivity for individual drugs ranged from 76·5% (52·5-92·3) for capreomycin to 99·1% (98·3-99·7) for rifampicin; specificity ranged from 93·1% (88·0-96·3) for ethambutol to 99·4% (98·3-99·8) for amikacin. Diagnostic accuracy was similar for primary clinical samples and culture isolates overall and for rifampicin, isoniazid, ethambutol, streptomycin, and fluoroquinolones, and similar after excluding studies at high risk of bias (overall sensitivity 95·2% [95% CrI 91·7-97·1] and specificity 98·6% [97·4-99·3]).

INTERPRETATION: Targeted NGS is highly sensitive and specific for detecting drug resistance across panels of tuberculosis drugs and can be performed directly on clinical samples. There is a paucity of data on performance for some currently recommended drugs. The barriers preventing the use of targeted NGS to diagnose drug-resistant tuberculosis in high-burden countries need to be addressed.

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PMID: 38795712 [Indexed for MEDLINE]

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

PubMed Non Open Access

53. Linezolid Pharmacokinetic-Anemia Modeling in Children with Rifampicin-Resistant Tuberculosis.

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Brooks JT(1), Solans BP(2)(3), Béranger A(2)(3)(4), Schaaf HS(5), van der Laan L(5)(6), Sharma S(7), Furin J(8), Draper HR(9), Hesseling AC(9), Garcia-Prats AJ(10)(5), Savic RM(2)(3).

Author information:
(1)University of California San Francisco School of Pharmacy, San Francisco, CA, United States of America.
(2)University of California San Francisco Schools of Pharmacy and Medicine, San Francisco, California, United States of America.
(3)UCSF Center for Tuberculosis, University of California San Francisco, San Francisco, CA, United States of America.
(4)URP7323 Pharmacologie et Évaluation des Thérapeutiques Chez l'Enfant et la Femme Enceinte, 21 Université Paris Cité, Paris, France.
(5)Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University. Cape Town, South Africa.
(6)Division of Clinical Pharmacology, Department of Medicine, University of Cape Town, Cape Town, South Africa.
(7)Department of Pediatrics, National Institute of Tuberculosis and Respiratory Diseases, New Delhi, India.
(8)Department of Global Health and Social Medicine, Harvard Medical School, Boston, MA, United States of America.
(9)Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University. Cape Town, South Africa.
(10)Department of Pediatrics, University of Wisconsin-Madison, School of

Medicine and Public Health, Madison, Wisconsin, USA.

BACKGROUND: Linezolid, an important component of rifampicin- and multidrug-resistant tuberculosis (RR/MDR-TB) treatment, is associated with treatment-limiting toxicities, including anemia. Patient-level and linezolid pharmacokinetic risk factors for anemia have not been well described in children treated for RR/MDR-TB.
METHODS: We evaluated the pharmacokinetics of linezolid and longitudinal hemoglobin data to validate an existing population linezolid pharmacokinetic model. We assessed the impact of linezolid pharmacokinetics and the risk of developing anemia in a prospectively enrolled cohort of children. The validation of a previously published population pharmacokinetic linezolid model used nonlinear mixed effects modeling. A multivariable ordinal logistic regression model was built to predict the incidence of anemia.
RESULTS: A total of 112 children, median age 7.2 (IQR: 2.2-16.3) years, were included from South Africa (n=87) and India (n=25). Of these, 24 children contributed new linezolid pharmacokinetic data. The population pharmacokinetic model which informs the currently recommended linezolid dosing in children (10-15 mg/kg) was validated with these additional new data. For every 1 g/dL lower baseline hemoglobin, the odds of developing grade 3 or 4 anemia increased by 2.64 (95% CI 1.98-3.62). For every 1 mg/L*h higher linezolid area under the concentration-time curve (AUC), the odds of developing a grade 3 or 4 anemia increased by 1.012 (95% CI 1.007-1.017).
CONCLUSIONS: These data taken together, confirm currently recommended linezolid doses in children. The risk of anemia in children should be carefully considered and monitored throughout. Initiating linezolid in children with low baseline hemoglobin increases the probability of experiencing grade 3 or 4 anemia.

DOI: 10.1093/cid/ciae497
PMID: 39422476

54. Management implications of latent TB among under-five children at risk: Insights from a community study in Mumbai, India.

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Surve S(1), Bhor V(2), Gounder V(1), Munne K(1), Begum S(3), Naukariya K(1), Gomare M(4), Puri V(4), Tipre P(4), Sutar N(4), Dhawale A(4), Naik R(4), Jaiswal A(5), Bhonde G(2), Shikhare M(1), Kamble R(1), Dalvi R(1), Kamat S(1), Tryambake V(1), Chauhan S(6), Shah I(5).

Author information:
(1)Department of Child Health Research, Indian Council of Medical Research - National Institute for Research in Reproductive and Child Health (ICMR-NIRRCH), Mumbai, India.
(2)Department of Molecular Immunology and Microbiology, Indian Council of Medical Research - National Institute for Research in Reproductive and Child Health (ICMR-NIRRCH), Mumbai, India.
(3)Department of Biostatistics, Indian Council of Medical Research - National Institute for Research in Reproductive and Child Health (ICMR-NIRRCH), Mumbai, India.
(4)Municipal Corporation of Greater Mumbai, Parel, Mumbai, India.
(5)Pediatric TB Clinic, Department of Pediatric Infectious Diseases, Bai Jerbai Wadia Hospital for Children, Mumbai, India.
(6)Department of Clinical and Operational Research, Indian Council of Medical Research - National Institute for Research in Reproductive and Child Health (ICMR-NIRRCH), Mumbai, India.

BACKGROUND: Latent tuberculosis infection (LTBI) management is crucial to WHO's End TB Strategy. Indian guidelines recommend treating under-five children with household TB contacts after ruling out active TB, regardless of TBI testing. However, the precise LTBI burden among children in high TB burden settings like India is unknown. A community-based study in Mumbai's urban slums screened and managed under-five children at LTBI risk to understand its epidemiology and inform TB control interventions.
METHODS: Total 369 eligible under-five children were enrolled for the study. LTBI screening was done using Tuberculin skin test and Interferon gamma release assay. Active TB was ruled out before initiation of TB preventive therapy among LTBI positives. Statistical tests like chi-square, logistic regression analysis and Hosmer-Lemeshow test were used.
RESULTS: Overall, LTBI prevalence among under-five children was 12.4% by IGRA and 21.4% by TST. Undernourished children had significantly lower LTBI positivity by IGRA ($p = 0.027$), while those with household contacts, longer contact duration and drug-resistant tuberculosis (DR-TB) exhibited proportionally greater IGRA positivity ($p = <0.001$).
CONCLUSION: The study found a lower LTBI prevalence among under-five children compared to adults, with key risk factors being HHC, DR-TB contact, and prolonged exposure. These findings suggest the need to revise or revisit the TPT framework for this age group in India, particularly by implementing a test-and-treat approach.

DOI: 10.1002/ppul.27336
PMID: 39422171

55. Drug-induced liver injury associated with pretomanid, bedaquiline, and linezolid: Insights from FAERS database analysis.

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He Q(1), Li Y(2), Liu S(1), Xue H(3), Xiang X(1), Wang T(4), Feng Z(4).

Author information:
(1)Department of Clinical Pharmacy and Pharmacy Administration, School of Pharmacy, Fudan University, Shanghai, China.
(2)Department of Infectious Diseases, Shanghai Key Laboratory of Infectious Diseases and Biosafety Emergency Response, National Medical Center for Infectious Diseases, Huashan Hospital, Shanghai Medical College, Fudan University, Shanghai, China.
(3)State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai, China.
(4)Department of Pharmacy, the Affiliated Hospital of Xuzhou Medical University, Xuzhou, Jiangsu, China.

AIMS: The emergence of drug-resistant tuberculosis has necessitated novel treatments like the pretomanid, bedaquiline and linezolid (BPaL) regimen. This study investigated the association of drug-induced liver injury (DILI) with the BPaL regimen compared to first-line antituberculosis drugs (isoniazid, rifampin, pyrazinamide and ethambutol [HRZE]).
METHODS: A retrospective pharmacovigilance analysis was conducted using data from the US Food and Drug Administration Adverse Event Reporting System database from July 2019 to June 2023. Disproportionality analysis was employed to calculate the reporting odds ratio (ROR) of DILI for each component of the BPaL regimen. Onset time and mortality rates of DILI across different regimens were also compared.
RESULTS: We identified 1242 cases of BPaL-related DILI. Most cases occurred in individuals under 65 years of age (63.8%), with more male patients affected than females (51.4% vs 39.5%). The association between antituberculosis drugs and DILI was stronger for the HRZE regimen (ROR = 7.99, 95% confidence interval [CI] 7.74-8.25) than the BPaL regimen (ROR = 4.75, 95% CI 4.55-4.97). The median onset time for DILI was significantly shorter with the BPaL regimen (8 days, interquartile range [IQR] 3-28) compared to the HRZE regimen (20 days, IQR 6-48) ($P < .001$). Additionally, the BPaL regimen was associated with a higher risk of death due to DILI compared to the HRZE regimen (14.1% vs 10.4%, $P = .003$).
CONCLUSIONS: Although the BPaL regimen had a lower overall risk of DILI compared to the HRZE regimen, it was significantly associated with DILI, indicating a need for careful monitoring during treatment.

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PMID: 39419512

56. Engineered Mycobacteriophage TM4::GeNL Rapidly Determines Bedaquiline, Pretomanid, Linezolid, Rifampicin, and Clofazimine Sensitivity in Mycobacterium tuberculosis Clinical Isolates.

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Rajagopalan S(1), Rourke AK(2), Asare E(1), Kohlerschmidt DJ(2), Das L(1), Ngema SL(3), Mulholland CV(1), Vilchèze C(1), Mahalingam V(1), Moodley S(4), Truebody B(4), Mackenzie J(4), Steyn AJC(4)(5), Perumal R(3)(6), Berney M(1), Larsen MH(1), O'Donnell MR(7)(8), Escuyer VE(2), Jacobs WR Jr(1).

Author information:
(1)Department of Microbiology and Immunology, Albert Einstein College of Medicine, Bronx, New York, USA.
(2)Wadsworth Center, New York State Department of Health, Albany, New York, USA.
(3)South African Medical Research Council-CAPRISA HIV-TB Pathogenesis and Treatment Research Unit, Centre for the AIDS Programme of Research in South Africa, Durban, South Africa.
(4)Africa Health Research Institute, University of KwaZulu-Natal, Durban, South Africa.
(5)Department of Microbiology, University of Alabama at Birmingham, Birmingham, Alabama, USA.
(6)Department of Pulmonology and Critical Care, University of KwaZulu-Natal, Durban, South Africa.
(7)Division of Pulmonary, Allergy, and Critical Care Medicine, Columbia University Medical Center, New York, New York, USA.
(8)Department of Epidemiology, Mailman School of Public Health, Columbia University Medical Center, New York, New York, USA.

BACKGROUND: Drug-resistant tuberculosis is a growing public health threat, and early characterization of the resistance phenotype is essential for guiding treatment and mitigating the high mortality associated with the disease. However, the slow growth rate of Mycobacterium tuberculosis, the causative agent of tuberculosis, necessitates several weeks for conventional culture-dependent drug susceptibility testing (DST). In addition, there are no widely available molecular diagnostic assays for evaluating resistance to newer tuberculosis drugs or drugs with complex resistance mechanisms.
METHODS: We have developed a luciferase-based reporter mycobacteriophage assay

that can determine drug resistance within 48 hours. We engineered the TM4 mycobacteriophage to express green enhanced nanoluciferase (GeNL) cassette and optimized DST for bedaquiline, pretomanid, linezolid, clofazimine, and rifampicin using clinical M. tuberculosis isolates.
RESULTS: To assess the feasibility of this assay, we conducted a proof-of-principle study using 53 clinical M. tuberculosis isolates. TM4::GeNL phage DST effectively distinguished between sensitive and resistant isolates for bedaquiline and rifampicin at a concentration of 0.125 μg/mL. Optimal differentiation between sensitive and resistant isolates for pretomanid, clofazimine, and linezolid was achieved at concentrations of 0.5 μg/mL, 0.25 μg/mL, and 1 μg/mL, respectively. Additionally, TM4::GeNL DST identified low-level rifampicin resistance in clinical isolates even though they were classified as sensitive by Mycobacteria Growth Indicator Tube DST.
CONCLUSIONS: TM4::GeNL reporter phage DST offers a rapid method to identify M. tuberculosis drug resistance, including resistance to newer tuberculosis drugs.

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57. Levofloxacin activity at increasing doses in a murine model of fluoroquinolone-susceptible and -resistant tuberculosis.

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Maitre T(1)(2), Godmer A(1)(3), Mory C(4), Chauffour A(1), Mai TC(1), El Helali N(4), Aubry A(1)(3), Veziris N(1)(3).

Author information:
(1)Sorbonne Université, Centre d'Immunologie et des Maladies Infectieuses (Cimi-Paris), UMR 1135, Paris, France.
(2)Department of Pneumology and Reference Centre for Rare Lung Diseases,

Assistance Publique Hôpitaux de Paris, Tenon Hospital, Paris, France.
(3)Fédération de Bactériologie, Centre National de Référence des Mycobactéries, APHP, Sorbonne Université, Paris, France.
(4)Unité de Microbiologie Clinique et Dosage des Anti-infectieux, Groupe Hospitalier Paris-Saint-Joseph, Paris, France.

High-dose levofloxacin was explored in a clinical trial against multidrug-resistant tuberculosis and failed to show increased efficacy. In this study, we used a murine model to explore the efficacy of a dose increase in levofloxacin monotherapy beyond the maximum dose evaluated in humans. A total of 120 4-week-old female BALB/c mice were intravenously infected with 106 CFU of Mycobacterium tuberculosis H37Rv wild-type (WT) or isogenic H37Rv mutants harboring GyrA A90V or D94G substitutions; the MICs were 0.25, 4, and 6 μg/mL, respectively. Levofloxacin 250 and 500 mg/kg were given every 12 h (q12h) orally for 4 weeks. Pharmacokinetic parameters were determined after five doses. These two regimens decreased lung bacillary load in mice infected with H37Rv WT but not in mice infected with the A90V and D94G mutants. Levofloxacin 250 mg/kg q12h in mice generated pharmacokinetic parameters equivalent to 1,000 mg/d in humans, whereas 500 mg/kg q12h generated a twofold greater exposure than the highest equivalent dose tested in humans (1,500 mg/d). In our dose-response model, the effective concentration at 50% (EC50) produced an AUC/MIC (AUC0-24h/MIC) ratio of 167.9 ± 27.5, and at EC80 it was 281.2 ± 97.3. Based on this model, high-dose levofloxacin regimens above 1,000 mg/d are not expected to cause a significant increase in bactericidal activity. This study suggests no benefit of high-dose levofloxacin above 1,000 mg/d in the treatment of fluoroquinolone-susceptible or -resistant tuberculosis.

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58. Arenicolide Family Macrolides Provide a New Therapeutic Lead Combating Multidrug-resistant Tuberculosis.

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Hwang S(1), Heo BE(2), Nguyen TQ(2), Kim YJ(3), Lee SG(4), Huynh TH(1), Kim E(1), Jo SI(5), Baek MJ(1), Shin EK(1), Oh J(6), Park C(7), Yoon YJ(1), Park EJ(3), Kim KT(3), Ryoo S(8), Lee DG(8), Wood C(9), Woo M(9), Kim DD(1), Paik S(3), Jo EK(3), Jang J(2), Oh DC(10).

Author information:
(1)Seoul National University, College of Pharmacy, KOREA, REPUBLIC OF.
(2)Gyeongsang National University, Division of Life Science, KOREA, REPUBLIC OF.

(3)Chungnam National University College of Medicine and Graduate School of Medicine, Microbiology, KOREA, REPUBLIC OF.
(4)National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, UNITED STATES OF AMERICA.
(5)Institute of Korean Insect Life, Institute of Korean Insect Life, KOREA, REPUBLIC OF.
(6)Yale University, Chemistry, UNITED STATES OF AMERICA.
(7)Chonnam National University, School of Biological Sciences and Technology, KOREA, REPUBLIC OF.
(8)Masan National Tuberculosis Hospital, Clinical Research Center, KOREA, REPUBLIC OF.
(9)Pasteur Institute of Korea, Tuberculosis Research Laboratory, KOREA, REPUBLIC OF.
(10)Seoul National University, College of Pharmacy, Rm 525, Bldg 20, 1 Gwanak-ro, Gwanak-gu, 08826, Seoul, KOREA, REPUBLIC OF.

The emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains of Mycobacterium tuberculosis (Mtb) poses a significant threat to health globally. During searching for new chemical entities regulating MDR- and XDR-Mtb, chemical investigation of the black oil beetle gut bacterium Micromonospora sp. GR10 led to the discovery of eight new members of arenicolides along with the identification of arenicolide A (Ar-A, 1), which was a previously reported macrolide with incomplete configuration. Genomic analysis of the bacterial strain GR10 revealed their putative biosynthetic pathway. Quantum mechanics-based computation, chemical derivatizations, and bioinformatic analysis established the absolute stereochemistry of Ar-A and arenicolides D-K (Ar-D-K, 2-9) completely for the first time. Biological studies of 1-9 revealed their antimicrobial activity against MDR and XDR strains of Mtb. Ar-A had the most potent in vitro antimicrobial efficacy against MDR- and XDR-Mtb. Mechanistically, Ar-A induced ATP depletion and destabilized Mtb cell wall, thereby inhibiting growth. Notably, Ar-A exerted a significant antimicrobial effect against Mtb in macrophages, was effective in the treatment of Mtb infections, and showed a synergistic effect with amikacin (AMK) in a mouse model of MDR-Mtb lung infection. Collectively, our findings indicate Ar-A to be a promising drug lead for drug-resistant tuberculosis.

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PMID: 39400949

59. Detection of Rifampicin Resistance rpoB Gene Using GeneXpert MTB/RIF Assay in Pulmonary Tuberculosis Cases at Debre Tabor Comprehensive Specialized Hospital, Northwest Ethiopia.

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Sharew B(1), Berhan A(1), Almaw A(1), Erkihun M(1), Tiruneh T(1), Kiros T(1), Solomon Y(1), Wondmagegn M(1), Wondimu E(2), Teshager A(3), Bihonegn S(3), Tilahun M(4), Getie B(1).

Author information:
(1)Department of Medical Laboratory Science, College of Health Sciences, Debre Tabor University, Debre Tabor, Ethiopia.
(2)College of Veterinary Medicine, Bonga University, Bonga, Ethiopia.
(3)Debre Tabor Comprehensive Specialized Hospital, Debre Tabor, Ethiopia.
(4)Department of Medical Laboratory Science, College of Medicine and Health Sciences, Wollo University, Wollo, Ethiopia.

BACKGROUND: Tuberculosis (TB) is a preventable and treatable disease leading to the second death globally. The evolution of drug resistance in Mycobacterium tuberculosis (MTB), particularly rifampicin resistance (RR), has hampered TB control efforts. Thus, this study aimed to provide information regarding the magnitude of MTB and rifampicin resistance among patients tested using the GeneXpert method.
METHODS: A retrospective analysis was carried out at DTCSH. The study included TB registration logbook data from all patients who visited the hospital and were tested for MTB with the Xpert MTB/RIF assay from 2017 to 2024. The laboratory-based data were entered, cleaned, and analyzed using SPSS version 26 software. Multilogistic regression analysis was employed, and a p value ≤ 0.05 was considered statistically significant.
RESULTS: A total of 12,981 patient results were included, of which 8.9% (1160/12,981) were MTB-positive and 7.1% (82/1160) were RR. Individuals aged 15-29 years (AOR = 2.13; 95% CI = 1.55-2.93, p < 0.001), living in rural areas (AOR = 1.23; 95% CI = 1.08-1.41, p = 0.003), and HIV+ (AOR = 1.79; 95% CI = 1.48-2.33, p < 0.001) had a higher risk of developing tuberculosis. While RR was identified in 63.4% (52/82) of new, 24.4% (20/82) of re-treated, and 12.2% (10/82) of failed presumptive TB patients.
CONCLUSION: In this study, MTB and RR trends were high. Productive age groups, rural populations, and HIV patients were at risk. To lessen the burden of this contagious and fatal disease, it is recommended to increase early diagnosis of drug-resistant TB and enhance infection control.

DOI: 10.1002/jcla.25111

PMID: 39387506

60. Clinical research for saliva-based therapeutic drug monitoring of linezolid.

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Inoue Y(1), Kashiwagi H(2), Sato Y(2), Nashimoto S(2), Endo T(3), Takahata M(4), Komatsu M(5), Sugawara M(2)(6)(7), Takekuma Y(6).

Author information:
(1)Graduate School of Life Science, Hokkaido University, Sapporo, Japan.
(2)Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo, Japan.
(3)Department of Orthopaedic Surgery, Hokkaido University Graduate School of Medicine, Sapporo, Japan.
(4)Department of Orthopaedic Surgery, Dokkyo Medical University, Tochigi, Japan.
(5)Department of Orthopaedic Surgery, Hokkaido Spinal Cord Injury Center, Bibai, Japan.
(6)Department of Pharmacy, Hokkaido University Hospital, Sapporo, Japan.
(7)Global Station for Biosurfaces and Drug Discovery, Hokkaido University, Sapporo, Japan.

AIMS: Linezolid is primarily used to treat of methicillin-resistant Staphylococcus aureus and multidrug-resistant tuberculosis infections. Thrombocytopenia due to linezolid usage is a concern, and therapeutic drug monitoring has been reported to be effective in its prevention. Plasma concentrations provide valuable information for treatment decisions; however, collecting plasma samples can be burdensome for both patients and healthcare providers. Therefore, there is interest in saliva as an alternative for monitoring, considering its potential to replace plasma samples.
METHODS: Patients hospitalized at Hokkaido University Hospital and Hokkaido Spinal Cord Injury Center between April 2022 and July 2024, who received oral or intravenous linezolid treatment, were enrolled. The concentrations of linezolid were simultaneously measured in plasma and saliva samples. We determined the concentration profiles of linezolid in the saliva and examined the correlation between saliva and plasma linezolid concentrations.
RESULTS: Eighteen patients receiving linezolid were enrolled. The average of saliva/plasma (S/P) concentration ratios of linezolid were 1.018. A strong correlation was found between the salivary and plasma concentrations of linezolid ($R = .833$, $P < .001$). Notably, in patients receiving intravenous administration of linezolid, the correlation was even more pronounced ($R = .885$, $P < .001$). Additionally, when focusing on the S/P ratio of the trough concentrations in the morning and at night, the S/P ratios at night were much closer to 1.0.
CONCLUSION: The concentrations of linezolid in plasma and saliva were similar,

indicating their potential applicability in clinical settings. The monitoring of linezolid concentrations in saliva has been shown to be particularly suitable for patients receiving intravenous administration.

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PMID: 39389066

61. Advancing against drug-resistant tuberculosis: an extensive review, novel strategies and patent landscape.

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Patel MN(1), Patel AJ(1), Nandpal MN(1), Raval MA(1), Patel RJ(1), Patel AA(1), Paudel KR(2), Hansbro PM(2), Singh SK(3), Gupta G(4)(5), Dua K(6), Patel SG(7).

Author information:
(1)Ramanbhai Patel College of Pharmacy, Charotar University of Science and Technology, CHARUSAT Campus, At. & Post:-Changa, Tal.:- Petlad, Dist.:- Anand, Gujarat, 388421, India.
(2)Centre for Inflammation, Faculty of Science, School of Life Sciences, Centenary Institute and University of Technology Sydney, Sydney, NSW, 2007, Australia.
(3)School of Pharmaceutical Sciences, Lovely Professional University, Phagwara, India.
(4)Centre for Research Impact & Outcome, Chitkara College of Pharmacy, Chitkara University, Rajpura, Punjab, 140401, India.
(5)Center of Medical and Bio-Allied Health Sciences Research, Ajman University, Ajman, United Arab Emirates.
(6)Discipline of Pharmacy, Graduate School of Health, University of Technology Sydney, Sydney, Australia.
(7)Ramanbhai Patel College of Pharmacy, Charotar University of Science and Technology, CHARUSAT Campus, At. & Post:-Changa, Tal.:- Petlad, Dist.:- Anand, Gujarat, 388421, India. samirpatel.ph@charusat.ac.in.

Drug-resistant tuberculosis (DR-TB) represents a pressing global health issue, leading to heightened morbidity and mortality. Despite extensive research efforts, the escalation of DR-TB cases underscores the urgent need for enhanced prevention, diagnosis, and treatment strategies. This review delves deep into the molecular and genetic origins of different types of DR-TB, highlighting recent breakthroughs in detection and diagnosis, including Rapid Diagnostic Tests like Xpert Ultra, Whole Genome Sequencing, and AI-based tools along with

latest viewpoints on diagnosis and treatment of DR-TB utilizing newer and repurposed drug molecules. Special emphasis is given to the pivotal role of novel drugs and discusses updated treatment regimens endorsed by governing bodies, alongside innovative personalized drug-delivery systems such as nano-carriers, along with an analysis of relevant patents in this area. All the compiled information highlights the inherent challenges of current DR-TB treatments, discussing their complexity, potential side effects, and the socioeconomic strain they impose, particularly in under-resourced regions, emphasizing the cost-effective and accessible solutions. By offering insights, this review aims to serve as a compass for researchers, healthcare practitioners, and policymakers, emphasizing the critical need for ongoing R&D to improve treatments and broaden access to crucial TB interventions.

DOI: 10.1007/s00210-024-03466-0
PMID: 39377922

62. QT Prolongation Associated with Administration of Bedaquiline, a Novel Anti-Tuberculosis Drug.

Cardiol Rev. 2024 Oct 8. doi: 10.1097/CRD.0000000000000790. Online ahead of print.

Gavras N(1), Schluger NW.

Author information:
(1)From the Department of Medicine, New York Medical College, Valhalla, NY.

Bedaquiline is a diarylquinoline compound that has recently been introduced and approved for use in the treatment of multidrug-resistant tuberculosis (MDR-TB). Its mechanism of action is inhibition of adenosine triphosphate-synthase. In combination with other antibiotics, bedaquiline-containing regimens administered for 6 months achieve cure rates of roughly 90%, in contrast to the previously used, 24-month-long WHO-recommended regimens for the treatment of MDR-TB. However, since its introduction, concerns have been raised about its effects on QT prolongation and its safety in routine clinical use. We reviewed the published experience regarding bedaquiline use, QT prolongation, and adverse cardiac events when the drug was used alone or in combination. Overall, data are reassuring that bedaquiline use in clinical practice is not associated with an excess of cardiac deaths or other clinically meaningful cardiac events. This review provides reassurance and support for the continued use of bedaquiline in the treatment of MDR-TB.

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PMID: 39377599

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63. Quantification of MDR-TB drug JBD0131 and its metabolite in plasma via UPLC-MS/MS: application in first-in-human study.

Bioanalysis. 2024 Oct 7:1-12. doi: 10.1080/17576180.2024.2404311. Online ahead of print.

Gao T(1)(2), Ou X(1)(2), Miao J(2), Qin Y(1)(2).

Author information:
(1)Department of Pharmacy, West China Hospital, Sichuan University, Chengdu, 610041, China.
(2)NMPA Key Laboratory for Clinical Research and Evaluation of Innovative Drug, Clinical Trial Center, West China Hospital, Sichuan University, Chengdu, 610041, China.

Aim: JBD0131, a novel anti-multidrug-resistant tuberculosis (MDR-TB) drug, can target and inhibit the synthesis of mycolic acids, which are crucial components of the cell wall of the Mycobacterium tuberculosis complex. To support the results of this clinical trial in healthy subjects, development of a specific and accurate quantification method for detecting JBD0131 and its metabolite DM131 in human plasma is needed.Materials & methods: Samples with prior added stabilizer were pretreated by protein precipitation method and the extracts were subjected to ultra-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS). The m/z transitions for the precursor/product ion pairs were 402.1/273 for JBD0131, 333.1/273 for DM131 and 386.1/257 for the internal standard (IS).Results: This method showed good linearity from 1 to 2000 ng/ml for JBD0131 and 0.25 to 500 ng/ml for DM131 and was validated in terms of selectivity, linearity, accuracy, precision, matrix effect, recovery of pretreament and stability.Conclusion: This method was sensitive and specific for measuring the plasma concentrations of JBD0131 and its metabolites. And it was applied for the investigation of the pharmacokinetics of JBD0131 and DM131 in a clinical trial.

Plain Language Summary: [Box: see text].

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PMID: 39373613

64. 3,5-disubstituted pyridines with potent activity against drug-resistant Mycobacterium tuberculosis clinical isolates.

Future Med Chem. 2024 Oct 3:1-19. doi: 10.1080/17568919.2024.2403963. Online ahead of print.

Sangu KG(1)(2), Azger Dusthackeer VN(3), Singh VK(1), Maykalwar S(1)(2), Krishna EV(2)(4), Angayarkanni B(3), Maitra R(5), Chopra S(2)(5), Misra S(2)(4), Rode HB(1)(2).

Author information:
(1)Department of Natural Products & Medicinal Chemistry, CSIR - Indian Institute of Chemical Technology, Tarnaka, Hyderabad, 500 007, India.
(2)Academy of Scientific & Innovative Research (AcSIR), Ghaziabad, Uttar Pradesh, 201 002, India.
(3)Department of Bacteriology, National Institute for Research in Tuberculosis, Chennai, 600 031, India.
(4)Department of Applied Biology, CSIR - Indian Institute of Chemical Technology, Tarnaka, Hyderabad, 500 007, India.
(5)Department of Molecular Microbiology & Immunology, CSIR - Central Drug Research Institute, Sitapur Road, Janakipuram Extension, Lucknow, Uttar Pradesh, 226 031, India.

Aim: We designed and synthesized a series of compounds with a 3,5-disubstituted pyridine moiety and evaluated them against Mycobacterium tuberculosis (Mtb) and drug-resistant Mtb clinical isolates.Methodology: A library of 3,5-disubstituted pyridine was synthesized. The compounds were screened for activity against M. tuberculosis H37Rv. The optimal substitutions needed for the activity were identified through structure-activity relationship (SAR) studies.Results: From the screening studies, compounds 24 and 26 were identified as potent members of this series with Minimum Inhibitory Concentration (MIC) of 1.56 µg/ml against M. tuberculosis H37Rv. These compounds did not show any inhibition against a panel of ESKAPE pathogens at >50 µg/ml indicating their selective killing of M. tuberculosis H37Rv. Importantly, compound 24 showed a selectivity index of 54.64 against CHO-K1 and 78.26 against VERO cell lines, while compound 26 showed a selectivity index of 108.5 against CHO-K1 and 63.2 against VERO cell lines, respectively. Compound 24 formed a stable complex with the target protein DprE1 with predicted binding energy -8.73 kcal/mol and inhibited multidrug-resistant clinical isolate of M. tuberculosis at 6.25 µg/ml.Conclusion: This study identified the 3,5-disubstituted pyridine derivative 24 with potent antituberculosis activity and can be taken forward to generate new preclinical

candidate.

Plain Language Summary: [Box: see text].

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PMID: 39363626

65. Sputum culture conversion and its predictors among drug-resistant pulmonary tuberculosis patients in eastern Ethiopia.

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Gamachu M(1)(2), Deressa A(3), Regassa LD(3), Bayu M(1), Mussa I(3), Kumsa FA(3)(4), Dingeta T(3).

Author information:
(1)School of Medicine, College of Health and Medical Sciences, Haramaya University, Harar, Ethiopia.
(2)Department of Public Health, Rift Valley University, Harar, Ethiopia.
(3)School of Public Health, College of Health and Medical Sciences, Haramaya University, Harar, Ethiopia.
(4)School of Population and Public Health, University of British Columbia, Vancouver, BC, Canada.

BACKGROUND: Evidence of time to culture conversion is used to predict the time of cure from the disease and the overall drug-resistant tuberculosis (TB) treatment duration. Even though evidence about sputum culture conversion is enormous in TB treatment, no study has yet been done in our areas, where cases are common. The study aimed to assess the time to sputum conversion and its predictors among drug-resistant TB patients from October 2013 to September 2021 in eastern Ethiopia.
METHODOLOGY: A retrospective cohort study was conducted in eastern Ethiopia among 273 drug-resistant TB patients who were treated from October 2013 to September 2021 at Dire Dawa City and Harari regional treatment centres. The Kaplan-Meier method was used to estimate the median time of sputum culture conversion. Cox proportional hazards regression was employed to detect the predictors of sputum culture conversion. An adjusted hazard ratio (aHR) with 95% confidence interval (CI) was used to determine the strength and significance of the association.
RESULTS: Of the 273 drug-resistant TB patients, the sputum culture of 216 (79.12%) patients became negative in a median time of 3 months (interquartile range 2-7). The time to sputum culture conversion was negatively associated with underweight (aHR 0.65 [95% CI 0.49 to 0.90]) and poor adherence (aHR 0.41 [95%

CI 0.24 to 0.69]). The time to sputum culture conversion was also positively associated with patients resistant to two or more drugs (aHR 1.58 [95% CI 1.07 to 2.32]) and patients receiving a short treatment regimen (aHR 2.24 [95% CI 1.10 to 2.55]).
CONCLUSIONS: A shorter culture conversion rate was observed compared with the median time recommended by the World Health Organization. Being underweight, poor adherence to treatment, resistance to two or more drugs and receiving a short treatment regimen were found to be predictors of time to sputum culture conversion. Implementing nutrition assessment, counselling and support of drug adherence may improve sputum culture conversion.

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PMID: 39348935

66. Whole-genome sequencing drug susceptibility testing is associated with positive MDR-TB treatment response.

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Larsson L(1), Corbett C(2), Kalmambetova G(3), Utpatel C(4), Ahmedov S(5), Antonenka U(2), Iskakova A(6), Kadyrov A(7), Kohl TA(4), Barilar V(4), Sahalchyk E(2), Niemann S(4), Hoffmann H(8), Kranzer K(9).

Author information:
(1)The Health Research Unit Zimbabwe, Biomedical Research and Training Institute, Harare, Zimbabwe;, Institute of Infectious Diseases and Tropical Medicine, Klinikum der Ludwig-Maximilians-Universität, Munich, Germany.
(2)Institute of Microbiology & Laboratory Medicine, IML red GmbH, WHO - Supranational Tuberculosis Reference Laboratory, Munich-Gauting, Germany.
(3)Republican Tuberculosis Center, National Tuberculosis Project Management, Bishkek, Kyrgyz Republic;, National Tuberculosis Reference Laboratory, Bishkek, Kyrgyz Republic.
(4)Research Center Borstel, Leibniz Lung Center, Molecular and Experimental Mycobacteriology, Borstel, Germany;, German Center for Infection Research, Partner Site Hamburg-Lübeck-Borstel-Riems, Borstel, Germany.
(5)USAID, Bureau for Global Health, TB Division, Washington, DC, USA.
(6)National Tuberculosis Reference Laboratory, Bishkek, Kyrgyz Republic.
(7)Republican Tuberculosis Center, National Tuberculosis Project Management, Bishkek, Kyrgyz Republic.
(8)Institute of Microbiology & Laboratory Medicine, IML red GmbH, WHO - Supranational Tuberculosis Reference Laboratory, Munich-Gauting, Germany;,

SYNLAB Gauting, SYNLAB MVZ Dachau, Munich-Gauting, Germany.
(9)The Health Research Unit Zimbabwe, Biomedical Research and Training Institute, Harare, Zimbabwe;, Institute of Infectious Diseases and Tropical Medicine, Klinikum der Ludwig-Maximilians-Universität, Munich, Germany;, Department of Clinical Research, London School of Hygiene & Tropical Medicine, London, UK.

<sec><title>BACKGROUND</title>Until recently, multidrug-resistant TB (MDR-TB) was treated with lengthy and toxic regimens. New three-drug anti-TB regimens raise the question of whether they are sufficiently active for MDR-TB in Central Asia, an MDR-TB hotspot region.</sec><sec><title>METHODS</title>In a cohort of rifampicin-resistant (RR) and MDR-TB patients in the Kyrgyz Republic, we investigated the impact of the number of drugs that were tested susceptible by whole-genome sequencing (WGS) and conventional drug susceptibility testing (DST) and used for treatment on the treatment response, defined as 'matches'. Logistic regressions were performed to assess the effect of having ≥ 4 susceptible drugs in a regimen at baseline and at Month 2 on the treatment response.</sec><sec><title>RESULTS</title>The study included 227 participants with RR/MDR-TB (30.8% female; median age 30.4 years). The age- and sex-adjusted analysis showed an association between a regimen with ≥ 4 WGS matches at baseline (adjusted odds ratio [aOR] 2.10, 95% CI 1.00-4.41). No association was found when using conventional DST to define matches.</sec><sec><title>CONCLUSION</title>Our study confirms that the inclusion of four efficacious anti-TB drugs in an MDR-TB regimen increases the chances of a positive treatment response. Susceptibility of at least four drugs in WGS-DST predicts a positive treatment response.</sec>.

DOI: 10.5588/ijtld.24.0052
PMID: 39334545 [Indexed for MEDLINE]

67. Challenges and Potential Solutions for Cycloserine Dosing in Patients With Sepsis Undergoing Continuous Renal Replacement Therapy.

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Zhang R(1), Qiu J(2), Zhou F(1), Cheng J(1), Fan X(1), Yan C(2), Zheng R(1), Cai X(1), Li J(3).

Author information:
(1)Department of Pharmacy, Zhejiang Hospital of Integrated Traditional Chinese and Western Medicine, Hangzhou, Zhejiang Province, China.
(2)Department of Tuberculosis ICU, Zhejiang Hospital of Integrated Traditional Chinese and Western Medicine, Hangzhou, Zhejiang Province, China.

(3)Department of Pharmacy, Zhejiang Hospital of Integrated Traditional Chinese and Western Medicine, Hangzhou, Zhejiang Province, China. Electronic address: jinmeng608@163.com.

Continuous kidney replacement therapy (CRRT) is a special form of dialysis, which has more significant advantages than traditional intermittent hemodialysis in treating critically ill patients. The impact of CRRT and disease complexity on drug clearance in critically ill patients has been reported in several studies; nevertheless, the pharmacokinetic changes of cycloserine in patients with sepsis undergoing CRRT have not been reported. Here, we report a case of a 52-year-old man with septic shock and severe multidrug-resistant tuberculosis who underwent anti-tuberculosis (anti-TB) therapy. The patient's anti-TB regimen included linezolid, clofazimine, cycloserine, and bedaquiline. Following continuous administration for 14 days, the patient was treated with CRRT due to acid-base imbalance and acute renal failure. Blood samples were collected at 0, 2, 4, 6, 10, and 12 hours following cycloserine administration (CRRT was initiated 2 hours after administration). Changes in plasma concentration of cycloserine before and after CRRT were measured. The peak concentration of cycloserine was 39.93 mg/L with a trough concentration of 7.90 mg/L, and the AUC0-12h was 294.36 mg·h/L. These findings suggest that the pharmacokinetics of cycloserine may be influenced by sepsis and CRRT therapy, and that cycloserine doses may need to be increased during CRRT therapy in patients with sepsis.

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PMID: 39321892

68. Mutations in Rv0678, Rv2535c, and Rv1979c Confer Resistance to Bedaquiline in Clinical Isolates of Mycobacterium Tuberculosis.

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Balgouthi K(1), AlMatar M(2), Saghrouchni H(1), Albarri O(1), Var I(3).

Author information:
(1)Department of Biotechnology, Institute of Natural and Applied Sciences, Çukurova University, 01330, Balcalı, Adana, Türkiye.
(2)Biology Department, Faculty of Education and Arts, Sohar University, Sohar, 311, Sultanate of Oman.
(3)Department of Food Engineering, Agricultural Faculty, Çukurova University, Adana, Turkey.

INTRODUCTION: Reduced bedaquiline (BDQ) sensitivity to antimycobacterial drugs has been linked to mutations in the Rv0678, pepQ, and Rv1979c genes of Mycobacterium tuberculosis (MTB). Resistance-causing mutations in MTB strains under treatment may have an impact on novel BDQ-based medication regimens intended to reduce treatment time. Due to this, we investigated the genetic basis of BDQ resistance in Turkish TB patients with MTB clinical isolates. Furthermore, mutations in the genes linked to efflux pumps were examined as a backup resistance mechanism.
METHODS: We scrutinized 100 MTB clinical isolates from TB patients using convenience sampling. Eighty MDR and twenty pan-drug susceptible MTB strains were among these isolates. Sequencing was performed on all strains, and genomic analyses were performed to find mutations in BDQ resistance-associated genes, including Rv0678 and pepQ(Rv2535c), which correspond to a putative Xaa-Pro aminopeptidase, and Rv1979c. Of the 74 isolates with PepQ (Rv2535c) mutations, four isolates (2.96%) exhibited MGIT-BDQ susceptibility.
RESULTS: Twenty-one (19.11%) of the ninety-one isolates carrying mutations, including Rv1979c, were MGIT-BDQ-sensitive. Nonetheless, out of the 39 isolates with Rv0678 mutations, four (2.96%) were sensitive to MGIT-BDQ. It was found that resistance-associated variants (RAVs) in Rv0678, pepQ, and Rv1979c are often linked to BDQ resistance.
CONCLUSION: In order to include variations in efflux pump genes in genome-based diagnostics for drug-resistant MTB, further evidence about their involvement in resistance is needed.

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69. [Emergence of a multidrug-resistant tuberculosis through inadequate treatment of isoniazid monoresistance].

Dtsch Med Wochenschr. 2024 Oct;149(20):1222-1226. doi: 10.1055/a-2369-3807. Epub 2024 Sep 23.

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

Früh J(1), Strasen J(1), Held M(1).

Author information:
(1)Pneumologie, Klinikum Würzburg-Mitte gGmbH, Standort Missioklinik, Würzburg, Deutschland.

HISTORY: We admitted a 65-year-old patient with suspected reactivation of a pulmonary tuberculosis for further diagnosis.
FINDINGS AND DIAGNOSIS: 14 months after completing a standard treatment course against pulmonary tuberculosis, the patient presented with cough and night sweat. A CT-scan revealed signs of a bipulmonary progress. Microbiological results proved multi-drug resistant tuberculosis (resistances against isoniazid and rifampicin). Reviewing the patient's old records uncovered a previous isoniazid-resistance at the start of the first treatment course, which had not been appropriately addressed.
THERAPY AND COURSE: The patient was started on oral therapy with Bedaquiline, Linezolid, Terizidon and Levofloxacin.
CONCLUSION: Treating tuberculosis, considering drug resistances is crucial. To avoid ineffective therapy, molecular diagnostic methods are recommended, however, cultural testing remains essential. Diagnostic latency, rising rates of drug resistances and lengthy treatment courses contribute to the complexity of treatment. In Germany, specialized outpatient clinics are available since 2014 for diagnosis and treatment of patients with tuberculosis or non-tuberculous mycobacterial diseases, even in the event of mere suspicion.

Publisher: ANAMNESE: Eine 65-jährige Patientin wurde aufgrund des Verdachts einer reaktivierten Tuberkulose zur weiteren Diagnostik zugewiesen.
UNTERSUCHUNG UND DIAGNOSE: Radiologisch zeigte sich rund 14 Monate nach abgeschlossener Standardtherapie einer pulmonalen Tuberkulose ein bipulmonaler Progress. Klinisch bestanden Husten und Nachtschweiß. Mikrobiologisch wurde eine multiresistente Tuberkulose (Resistenzen gegen Isoniazid und Rifampicin) nachgewiesen. Nach Aktendurchsicht fiel auf, dass bereits bei initialer Diagnose eine Resistenz gegen Isoniazid bestand, welche therapeutisch nicht berücksichtigt worden war.
THERAPIE UND VERLAUF: Eine für 18 Monate geplante orale Therapie mit Bedaquilin, Linezolid, Terizidon und Levofloxacin wurde eingeleitet.
FOLGERUNG: Bei der Therapie einer Tuberkulose müssen Resistenzen unbedingt bedacht werden. Um eine ineffektive Therapie zu vermeiden, sollte auch molekulare Diagnostik eingesetzt werden; Kulturbefunde sind jedoch immer anzustreben. Durch diagnostische Latenz, zunehmende Resistenzen und eine lange Therapiedauer ist die Behandlung der Tuberkulose komplex. Seit 2014 gibt es aus diesem Grund die Möglichkeit, Patienten mit Tuberkulose oder atypischer Mykobakteriose (auch bei Verdacht) in Ambulanzen der spezialfachärztlichen Versorgung (ASV) zu behandeln.

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Conflict of interest statement: Die Autorinnen/Autoren geben an, dass kein Interessenkonflikt besteht.

70. Pharmacokinetics of anti-TB drugs in children and adolescents with drug-resistant TB: a multicentre observational study from India.

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Agibothu Kupparam HK(1), Shah I(2), Chandrasekaran P(3), Mane S(4), Sharma S(5), Thangavelu BR(1), Vilvamani S(1), Annavi V(1), Mahalingam SM(1), Thiruvengadam K(6), Navaneethapandian PG(3), Gandhi S(2), Poojari V(2), Nalwalla Z(2), Oswal V(7), Giridharan P(8), Babu SB(9), Rathinam S(10), Frederick A(11), Mankar S(7), Jeyakumar SM(1).

Author information:
(1)Department of Clinical Pharmacology, ICMR-National Institute for Research in Tuberculosis, No.1 Mayor Sathiyamoorthy Road, Chetpet, Chennai 600 031, Tamil Nadu, India.
(2)Pediatric Infectious Diseases and Pediatric GI, Hepatology, Pediatric DR TB (State), Center of Excellence, Department of Pediatric Infectious Diseases, B.J. Wadia Hospital for Children, Mumbai, India.
(3)Department of Clinical Research, ICMR-National Institute for Research in Tuberculosis, No.1 Mayor Sathiyamoorthy Road, Chetpet, Chennai 600 031, Tamil Nadu, India.
(4)Department of Pediatrics, State Pediatric Center of Excellence for TB, Grant Government Medical College, Sir JJ Group of Hospitals, Mumbai, India.
(5)Department of Pediatrics, National Institute of Tuberculosis and Respiratory Diseases, New Delhi, India.
(6)Department of Epidemiology Statistics, ICMR-National Institute for Research in Tuberculosis, No.1 Mayor Sathiyamoorthy Road, Chetpet, Chennai 600 031, Tamil Nadu, India.
(7)DR-TB Site-Shatabdi Municipal Hospital, Govandi, Mumbai, India.
(8)Department of Epidemiology, ICMR-National Institute for Research in Tuberculosis, No.1 Mayor Sathiyamoorthy Road, Chetpet, Chennai 600 031, Tamil Nadu, India.
(9)Department of Pediatric Pulmonology, Institute of Child Health and Hospital for Children, Chennai, Tamil Nadu, India.
(10)Government Hospital of Thoracic Medicine, Chennai, Tamil Nadu, India.
(11)State TB Cell, Chennai, Tamil Nadu, India.

BACKGROUND: Drug-resistant tuberculosis (DR-TB) is one of the challenging forms of TB to treat, not only in adults but also in children and adolescents.
Further, there is a void in the treatment strategy exclusively for children due

to various reasons, including paucity of pharmacokinetic (PK) data on anti-TB drugs across the globe. In this context, the present study aimed at assessing the PK of some of the anti-TB drugs used in DR-TB treatment regimens.
METHOD: A multicentre observational study was conducted among DR-TB children and adolescents (n = 200) aged 1-18 years (median: 12 years; IQR: 9-14) treated under programmatic settings in India. Steady-state PK (intensive: n = 89; and sparse: n = 111) evaluation of moxifloxacin, levofloxacin, cycloserine, ethionamide, rifampicin, isoniazid and pyrazinamide was carried out by measuring plasma levels using HPLC methods.
RESULTS: In the study population, the frequency of achieving peak plasma concentrations ranged between 13% (for rifampicin) to 82% (for pyrazinamide), whereas the frequency of suboptimal peak concentration for pyrazinamide, cycloserine, moxifloxacin, levofloxacin and rifampicin was 15%, 19%, 29%, 41% and 74%, respectively. Further, the frequency of supratherapeutic levels among patients varied between 3% for pyrazinamide and 60% for isoniazid. In the below-12 years age category, the median plasma maximum concentration and 12 h exposure of moxifloxacin were significantly lower than that of the above-12 years category despite similar weight-adjusted dosing.
CONCLUSIONS: Age significantly impacted the plasma concentration and exposure of moxifloxacin. The observed frequencies of suboptimal and supratherapeutic concentrations underscore the necessity for dose optimization and therapeutic drug monitoring in children and adolescents undergoing DR-TB treatment.

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71. Nanoparticles target M2 macrophages to silence kallikrein-related peptidase 12 for the treatment of tuberculosis and drug-resistant tuberculosis.

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Wang Y(1), Liu Y(1), Long M(1), Dong Y(1), Li L(1), Zhou X(2).

Author information:
(1)National Key Laboratory of Veterinary Public Health and Safety, College of Veterinary Medicine, China Agricultural University, Beijing 100193, China.

(2)National Key Laboratory of Veterinary Public Health and Safety, College of Veterinary Medicine, China Agricultural University, Beijing 100193, China. Electronic address: zhouxm@cau.edu.cn.

Matrix metalloproteinases (MMPs) are involved in the breakdown of lung extracellular matrix and the consequent release of Mycobacterium tuberculosis into the airways. Recent studies indicate that kallikrein-related peptidase 12 (KLK12) regulate MMP-1 and MMP-9, suggesting that targeting the KLK12 gene could be a promising tuberculosis (TB) treatment. To maximise therapeutic potential, this strategy of silencing KLK12 needs to be delivered to the pathogenic cell population while preserving the immunoprotective and tissue homeostatic functions of other lung macrophages. Our research found that KLK12 is highly expressed in M2 macrophages, leading us to design mannose-based bovine serum albumin nanoparticles (MBNPs) for delivering siRNA to silence KLK12 in these cells. The results of in vitro experiments showed that MBNPs could accurately enter M2 macrophages and sustainably release KLK12-siRNA with the help of mannose and mannose receptor targeting. The results of the in vivo experiments showed that MBNPs could reach the lungs within 1 h after intraperitoneal injection and peaked at 6 h. MBNPs increased collagen fibre content in the lungs by decreasing the levels of KLK12/MMPs thereby limiting the progression of TB. Importantly, MBNPs provided greater alleviation of pulmonary TB symptoms and reduced bacterial load in both TB and drug-resistant TB models. These findings provide an alternative and effective option for the treatment of TB, especially when drug resistance occurs. STATEMENT OF SIGNIFICANCE: RNA interference using small interfering RNA (siRNA) can target various genes and has potential for treating diseases such as tuberculosis (TB). However, siRNAs are unstable in the blood and within cells. This study presents bovine serum albumin nanoparticles encapsulating KLK12-siRNA (BNPs) synthesized via desolvation. A mannose layer was added (MBNPs) to target mannose receptors on M2 macrophages, facilitating endocytosis. The low pH-responsive MBNPs enhance lysosomal escape for siRNA delivery, downregulating the KLK12 pathway. Tests confirmed that MBNPs effectively inhibited Mycobacterium bovis proliferation, reduced granulomas, and decreased inflammation in a mouse model. This research aims to reduce antibiotic use, shorten treatment duration, and provide a novel TB treatment option.

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

paper.

72. Evaluation of the STANDARD M10 MDR-TB and MTB/NTM assays for the detection of Mycobacterium tuberculosis, rifampicin and isoniazid resistance, and nontuberculous mycobacteria in a low-incidence setting.

J Clin Microbiol. 2024 Oct 16;62(10):e0040224. doi: 10.1128/jcm.00402-24. Epub 2024 Sep 19.

Luukinen B(1)(2)(3), Aittoniemi J(2), Miikkulainen-Lahti T(1), Mentula S(4), Pätäri-Sampo A(1).

Author information:
(1)Department of Clinical Microbiology, HUS Diagnostic Center, University of Helsinki and Helsinki University Hospital, Helsinki, Finland.
(2)Department of Clinical Microbiology, Fimlab Laboratories, Tampere, Finland.
(3)Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland.
(4)Department of Health Security, Finnish Institute for Health and Welfare, Helsinki, Finland.

Rapid detection is crucial for tuberculosis (TB) control. GeneXpert (Cepheid) is a widely used PCR system, known for its simplicity, random access, and point-of-care compatibility. SD BIOSENSOR recently introduced a similar system, STANDARD M10, including a Mycobacterium tuberculosis (MTB) and rifampicin (RIF) and isoniazid resistance (herein, MDR-TB) assay and an MTB/nontuberculous mycobacteria (NTM) assay. We evaluated these assays for the potential to replace the established Xpert MTB/RIF Ultra assay in a low-TB incidence setting. We analyzed 160 clinical respiratory samples (45 MTB-positive and 35 NTM-positive) and further 24 drug-resistant MTB, 30 mycobacterial species (2 MTB, 28 NTM), and 37 non-mycobacterial isolates. Compared with culture, clinical sensitivities and specificities for MTB detection were 88.9% (95% confidence interval [CI] = 76.1-95.6%) and 97.4% (CI = 92.3-99.4%) with Xpert Ultra, 88.9% (95% CI = 76.1-95.6%) and 98.3% (CI = 93.5-99.9%) with M10 MDR-TB, and 84.4% (CI = 70.9-94.4%) and 98.3% (CI = 93.5-99.9%) with M10 MTB/NTM, respectively. For NTM detection, M10 MTB/NTM showed sensitivity and specificity of 65.7% (CI = 49.1-79.2%) and 96.8% (CI = 91.8-99.0%). Compared with phenotypic drug susceptibility testing (DST), sensitivity and specificity for detecting RIF resistance were 100% (CI = 77.3-100%) and 95.6% (CI = 84.4-99.6%) with Xpert Ultra, and 100% (CI = 74.9-100%) and 95.5% (CI = 84.0-99.6%) with M10 MDR-TB. M10 MDR-TB showed 92.3% sensitivity (CI = 74.7-99.0%) and 100% specificity (CI = 87.3-100%) for detecting isoniazid resistance. All discrepancies in DST by PCR were concordant with whole-genome sequencing. While M10 MDR-TB demonstrated great potential as an alternative to Xpert Ultra, M10 MTB/NTM had limitations in

NTM screening. Additionally, the M10 sputum pretreatment did not inactivate MTB efficiently, which should be considered in process risk assessment.
IMPORTANCE: The molecular diagnostic STANDARD M10 system is highly analogous to the widely established GeneXpert system, which significantly increases the relevance of this evaluation study in the field of rapid detection of M. tuberculosis. To our knowledge, this is the first clinical evaluation describing the performance of the STANDARD M10 MDR-TB and MTB/NTM assays, including an extensive analytical specificity panel (inclusivity and exclusivity) for the detection of M. tuberculosis, drug resistance, and nontuberculous mycobacteria.

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73. Exploring the Chemical Space of Mycobacterial Oxidative Phosphorylation Inhibitors Using Molecular Modeling.

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Matar IK(1)(2), Dong Z(3), Matta CF(1)(2).

Author information:
(1)Department of Chemistry, Saint Mary's University, 923 Robie Street, B3H 3C3, Halifax, NS, Canada.
(2)Department of Chemistry and Physics, Mount Saint Vincent University, 166 Bedford Highway, B3M 2J6, Halifax, NS, Canada.
(3)Department of Biology, Saint Mary's University, 923 Robie Street, B3H 3C3, Halifax, NS, Canada.

Mycobacteria are opportunistic intracellular pathogens that have plagued humans and other animals throughout history and still are today. They manipulate and hijack phagocytic cells of immune systems, enabling them to occupy this peculiar infection niche. Mycobacteria exploit a plethora of mechanisms to resist antimicrobials (e. g., waxy cell walls, efflux pumps, target modification, biofilms, etc.) thereby evolving into superbugs, such as extensively drug-resistant tuberculosis (XDR TB) bacilli and the emerging pathogenic Mycobacterium abscessus complex. This review summarizes the mechanisms of action of some of the surging antimycobacterial strategies. Exploiting the fact that mycobacteria are obligate aerobes and the differences between their oxidative phosphorylation pathways versus their human counterpart opens a promising avenue for drug discovery. The polymorphism of respiratory complexes across

mycobacterial pathogens imposes challenges on the repositioning of antimycobacterial agents to battle the rise in nontuberculous mycobacterial infections. In silico strategies exploiting mycobacterial respiratory machinery data to design novel therapeutic agents are touched upon. The potential druggability of mycobacterial respiratory elements is reviewed. Future research addressing the health challenges associated with mycobacterial pathogens is discussed.

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PMID: 39302818

74. Tuberculosis vaccine - A timely analysis of the drawbacks for the development of novel vaccines.

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Jeyachandran DS(1), Pusam Y(2).

Author information:
(1)Lab in Biotechnology and Biosignal Transduction, Department of Orthodontics, Saveetha Dental College & Hospitals, Saveetha Institute of Medical and Technical Sciences (SIMATS), Saveetha University, Chennai, 77, Tamil Nadu, India. Electronic address: sivakamavalli.sdc@saveetha.com.
(2)PG & Research Department of Biotechnology & Microbiology, National College Autonomous, Tiruchirappalli, Tamil Nadu, India. Electronic address: yashikapusam09@gmail.com.

The BCG vaccine, Bacille Calmette Guerin, holds the distinction of being the most widely administered vaccine. Remarkably, a century has passed since its discovery; however, puzzlingly, questions persist regarding the effectiveness of the immune response it triggers. After years of diligent observation, it has been deduced that BCG imparts immunity primarily to a specific age group, namely children. This prompts a significant query: the rationale behind BCG's limited efficacy against TB in particular age groups and populations remains elusive. Beyond vaccinations, drug therapy has emerged as an alternative route for TB prevention. Nonetheless, this approach faces challenges in the contemporary landscape, marked by the emergence of new instances of MDR-TB and XDR-TB, compounded by the financial burden of treatment. It's noteworthy that BCG remains the sole WHO-approved vaccine for TB. This comprehensive review delves into several aspects, encompassing the immune response during infection, the shortcomings of BCG in conferring immunity, and the various factors contributing

to its limitations. Within this discourse, we explore potential explanations for the observed deficiencies of the BCG vaccine and consider how these insights could catalyze the development of future vaccines. The current landscape of novel vaccine development for TB is illuminated, including a spotlight on the latest vaccine candidates.

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PMID: 39278679 [Indexed for MEDLINE]

75. Comparative study of infection control practices in DOTS/sputum microscopy centre in two different districts of state of Uttarakhand and Uttar Pradesh of India.

Indian J Tuberc. 2024 Oct;71(4):421-428. doi: 10.1016/j.ijtb.2023.08.002. Epub 2023 Aug 7.

Ahmad P(1), Aroara VK(2).

Author information:
(1)Dept of Chest & TB, Santosh Medical College & University, Ghaziabad, UP, India. Electronic address: drparvez28@gmail.com.
(2)Santosh University, Ghaziabad, UP, India.

BACKGROUND & OBJECTIVE: Tuberculosis (TB) is endemic in India. TB is transmitted through droplet infection and the transmission occurs when a person inhales droplet nuclei containing of Mycobacterium tuberculosis. Infection control practices play a major role in controlling the TB infection in healthcare settings and further prevents TB infection in the HCWs. The aim of the study is to conduct the cross sectional study for infection control practices in DOTS cum Sputum Microscopy Centre's under NTEP in Ghaziabad (Uttar Pradesh) & Dehradun (Uttarakhand) districts with the objective to assess the compliance of infection control measures by HCWs in DOTS cum Sputum Microscopy Centre's and to suggest the suitable measures and/or model to reduce the transmission of infection to the HCWs and to the community at large.
MATERIALS & METHODS: The cross sectional study is conducted for two years in two districts of different state having high burden of TB disease in UP and low burden of disease in UK state. All DOTS cum Sputum Microscopy centres of both selected districts i.e. 100% sample size are covered in the study.
RESULTS: Hand washing is the most efficient and cost-effective practice for prevention and control of infection. In Dehradun district 66.66% (12) centers and in Ghaziabad district 57.14% (16) centers have adequate hand washing

facility available at DOTS and sputum microscopy lab. Unavailability of adequate PPE will lead to the infection. In Dehradun district, 55.56% (10) centers have adequate PPE available whereas in Ghaziabad District 21.43% (6) centers have adequate PPE available. Training on infection prevention and control for HCWs are provided in 27.78% (5) DOTS/sputum microscopy center in Dehradun whereas none of the DOTS/sputum microscopy center in Ghaziabad district are given training on infection prevention & control for HCWs in last one year. Adequate ventilation plays an important role in transmission of TB/MDR TB or any respiratory infection. HCWs working in DOTS/Sputum microscopy center are at risk to contact the TB/MDR TB infection if there is no proper ventilation in their working places. In 33.33% (6) DOTS/sputum microscopy center in Dehradun & 28.57% (8) in Ghaziabad district have adequate ventilation. Layout of DOTS room and for sputum microscopy center are suggested to reduce the risk of transmission of TB/MDR-TB and other respiratory pathogens amongst HCWs who are working in DOTS cum sputum microscopy center.
CONCLUSION: DOTS cum Sputum Microscopy Centers of both districts in different states are having deficient infection control practices. Staff is not adequately trained in infection prevention and control practices.

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PMID: 39278675 [Indexed for MEDLINE]

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

76. Detection of katG, inhA and ahpC gene mutation in clinical isolates of isoniazid-resistant Mycobacterium tuberculosis in Makassar City, South Sulawesi, Indonesia.

Indian J Tuberc. 2024 Oct;71(4):383-388. doi: 10.1016/j.ijtb.2023.03.019. Epub 2023 Apr 1.

Junaedi MA(1), Massi MN(2), Sjahril R(3), Halik H(4), Muttaqin Z(1), Rifqiani N(1), Safitri NI(1), Pratika M(1), Islam IC(1), Hamid F(5), Natzir R(6), Ahmad A(7).

Author information:
(1)Master Program of Biomedical Science,Graduate School, Hasanuddin University, Makassar, South Sulawesi, Indonesia.
(2)Department of Microbiology, Faculty of Medicine, Hasanuddin University, Makassar, South Sulawesi, Indonesia; Hasanuddin University Medical Research

Center, Makassar, South Sulawesi, Indonesia; Microbiology Laboratory, Hasanuddin University Hospital, Makassar, South Sulawesi, Indonesia; Hasanuddin University Teaching Hospital, Makassar, South Sulawesi, Indonesia. Electronic address: nasrumm@unhas.ac.id.
(3)Department of Microbiology, Faculty of Medicine, Hasanuddin University, Makassar, South Sulawesi, Indonesia; Hasanuddin University Medical Research Center, Makassar, South Sulawesi, Indonesia; Microbiology Laboratory, Hasanuddin University Hospital, Makassar, South Sulawesi, Indonesia; Hasanuddin University Teaching Hospital, Makassar, South Sulawesi, Indonesia.
(4)Hasanuddin University Medical Research Center, Makassar, South Sulawesi, Indonesia; Megarezky University, Makassar, South Sulawesi, Indonesia.
(5)Department of Microbiology, Faculty of Medicine, Hasanuddin University, Makassar, South Sulawesi, Indonesia.
(6)Department of Biochemistry, Faculty of Medicine, Hasanuddin University, Makassar, South Sulawesi, Indonesia.
(7)Department of Chemistry, Faculty of Mathematics and Natural Science, Hasanuddin University, Makassar, South Sulawesi, Indonesia.

BACKGROUND: Tuberculosis (TB) is an airborne disease caused by Mycobacterium tuberculosis (M. tuberculosis). The world is currently facing challenges due to the spread of anti-tuberculosis drug-resistant of M. tuberculosis. Isoniazid-resistant (INH), is one of the first-line anti-tuberculosis agents that has a high resistance case. This study used Multiplex allele-specific Polymerase Chain Reaction (MAS-PCR) to detect the most common mutations associated with isoniazid resistance on inhA, katG, and ahpC gene.
METHODS: This study used samples from clinical isolates of M. tuberculosis which had been tested for their antibiotic sensitivity of first-line anti-tuberculosis drugs. The DNA extraction process was carried out using the boiling method and then amplified with specific primers for inhA, katG, and ahpC genes using the MAS-PCR method. The results are then read on the electrophoretic gel with an interpretation of the mutation gene when the target gene DNA bands were absent according to the allele-specific fragments target.
RESULTS: A total of 200 isolates were tested in this study consisting of isoniazid-resistant and susceptible with the largest distribution of Multi-Drug Resistant (MDR) isolates with a total of 146 isolates (73%). The most significant gene mutation was on the ahpC gene in 61 isolates (30,5%) and the combination mutation of the katG + ahpC gene in 52 isolates (26%) with sensitivity and specificity of the test reaching 87% and 42% for the detection of INH-resistant.
CONCLUSION: Mutation on the ahpC gene has the highest percentage in this study. AhpC gene can be considered one of the essential genes to be tested for the cause of isoniazid-resistant. Using MAS-PCR for detecting gene mutation in isoniazid-resistant was simple and easy, it has the potential to be widely used as a rapid screening molecular test.

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PMID: 39278670 [Indexed for MEDLINE]

77. Nanopore-based targeted sequencing test for direct tuberculosis identification, genotyping, and detection of drug resistance mutations: a side-by-side comparison of targeted next-generation sequencing technologies.

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Cabibbe AM(#)(1), Moghaddasi K(#)(1), Batignani V(1), Morgan GSK(1), Di Marco F(1), Cirillo DM(1).

Author information:
(1)Emerging Bacterial Pathogens Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy.
(#)Contributed equally

We investigated the performance of the targeted next-generation sequencing (tNGS)-based Oxford Nanopore Diagnostics AmPORE TB assay, recently approved by the World Health Organization (WHO) as tuberculosis (TB) diagnostic test for the detection of drug resistance on respiratory specimens. A total of 104 DNA samples from Xpert MTB/RIF-positive TB sputum specimens were tested using the AmPORE TB kit, with the GenoScreen Deeplex Myc-TB as a comparative tNGS assay. For AmPORE TB, DNA samples were divided into five sequencing runs on the MinION device. Data analysis was performed using proprietary software. The WHO catalog of mutations was used for drug resistance interpretation. The assay achieved a high validity rate of 98% (102/104 DNA samples), homogeneous mean reads coverage across TB-positive specimens, and 100% positive and negative agreements for detecting mutations associated with resistance to rifampicin, pyrazinamide, fluoroquinolones, ethambutol, and capreomycin compared with Deeplex Myc-TB. The main discrepancies for the remaining drugs were attributable to the different assay panel designs. The AmPORE TB turnaround time was approximately 5-6 hours from extracted DNA to tNGS reporting for batches of 22 DNA samples. The AmPORE TB assay drastically reduced the time to tNGS reporting from days to hours and showed good performance for drug-resistant TB profiling compared with Deeplex Myc-TB.
IMPORTANCE: Targeted next-generation sequencing (tNGS) of Mycobacterium tuberculosis provides comprehensive resistance predictions matched to new multidrug-resistant/rifampicin-resistant tuberculosis regimens and received World Health Organization approval for clinical use in respiratory samples in

2024. The advanced version of the Oxford Nanopore Diagnostics AmPORE TB tNGS kit was evaluated in this study for the first time and demonstrated good performance, flexibility, and faster turnaround time compared with the existing solutions.

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PMID: 39240079 [Indexed for MEDLINE]

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

78. Association between experienced stigma, anxiety, depression and loneliness among people with drug-resistant tuberculosis in Lagos Nigeria: The moderating role of social support.

Trop Med Int Health. 2024 Oct;29(10):882-894. doi: 10.1111/tmi.14046. Epub 2024 Sep 5.

Adejumo OA(1)(2), Haffejee F(2), Jinabhai C(3), Daniel O(4).

Author information:
(1)Mainland Hospital Yaba, Lagos, Nigeria.
(2)Department of Basic Medical Sciences, Durban University of Technology, Durban, South Africa.
(3)Faculty of Health Sciences, Durban University of Technology, Durban, South Africa.
(4)Department of Community Medicine and Primary Care, Olabisi Onabanjo University, Sagamu, Nigeria.

BACKGROUND: This study assessed the moderating effect of social support on the association between experienced stigma versus anxiety, depression and loneliness among people with drug-resistant tuberculosis.
METHODS: A descriptive cross-sectional study was conducted among 203 adults on treatment for drug-resistant tuberculosis for at least 8 weeks. Validated scales were used to assess experienced stigma, anxiety, depression, loneliness and social support. Partial correlations and hierarchical multiple regression were used to determine the moderating effect of social support on the association between experienced stigma versus anxiety, depression and loneliness. The interaction was visualised using slope analysis.
RESULTS: Anxiety, loneliness and depression were reported by 148 (72.9%), 114 (56.2%) and 128 (63.1%) of the 203 participants, respectively. Experienced stigma was positively associated with depression ($B = 0.428$, $p < 0.001$), anxiety ($B = 0.374$, $p < 0.001$) and loneliness ($B = 0.285$, $p = 0.001$). Social support was

negatively associated with depression (B = -0.255, p < 0.001), anxiety (B = -0.406, p < 0.001) and loneliness (B = -0.270, p = 0.001). The impact of experienced stigma on depression was different at low (B = 0.567, SE = 0.115, p < 0.001) and high (B = 0.275, SE = 0.253, p = 0.024) groups of social support. Similarly, at low social support, the effect of experienced stigma on loneliness (B = 0.491, SE = 0.250, p < 0.001) and anxiety (B = 0.254, SE = 0.060, p = 0.044) was different compared to the effect of experienced stigma on loneliness (B = 0.275, SE = 0.253, p = 0.024) and anxiety (B = 0.127, SE = 0.094, p = 0.307) at high group of social support.
CONCLUSION: In this study, social support reduced the effects of experienced stigma on anxiety, depression and loneliness suggesting that improving social support among people with drug-resistant tuberculosis is crucial in reducing the negative effects of stigma on anxiety, depression and loneliness.

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PMID: 39233632 [Indexed for MEDLINE]

79. [Pre-extensively and extensively drug-resistant tuberculosis, in Libreville, Gabon].

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[Article in French]

Kombila UD(1), Manomba Boulingui C(2), N'Gomanda F(3), Mouity Mavoungou JV(3), Ngea Epossi CBH(3), Bivigou N(3), Tsioukaka S(3), Tshisekedi JDD(4), Mahoumbou J(4), Boguikouma JB(4).

Author information:
(1)Service de médecine interne, CHU de Libreville, faculté de médecine, université des sciences de la santé de Libreville, Libreville, Gabon; Faculté de médecine, université des sciences de la santé de Libreville, Libreville, Gabon. Electronic address: ulrichdavyk@gmail.com.
(2)Service d'infectiologie, CHU de Libreville, Libreville, Gabon; Faculté de médecine, université des sciences de la santé de Libreville, Libreville, Gabon.
(3)Service de médecine interne, CHU de Libreville, faculté de médecine, université des sciences de la santé de Libreville, Libreville, Gabon.
(4)Programme national de lutte contre la tuberculose (PNLT), Libreville, Gabon.

INTRODUCTION: Very few studies have been devoted to extensively drug-resistant (XDR) strains of Mycobacterium tuberculosis (TB) in Gabon.

AIM: The aim of the present study is to present the epidemiology of pre-XDR and XDR TB and the evolution over time of patients with multidrug-resistant TB.
METHODS: This retrospective study covered the activities from 2019 to 2022 of the Nkembo anti-tuberculosis center.
RESULTS: Fifteen patients were eligible, including 11 (73.3%) pre-XDR patients and 4 (26.7%) XDR-TB patients. Three (20.0%) patients had HIV/TB co-infection. The sample consisted of 7 men (46.7%) and 8 women (53.3%), a sex ratio (M/F) of 0.87. The average age was 35.6 years, and the median 34 years, with extremes of 23 and 60 years. Eight patients (53.3%) represented new cases of pre-XDR or XDR-TB tuberculosis. The majority (60%; n=9) came from deprived neighborhoods with widespread promiscuity. The therapeutic success rate among pre-XDR patients was 4 (36.4%) versus 2 (50.0%) among XDR-TB patients. Reported mortality occurred 5 (33.3%) patients during treatment, including 3 pre-XDR and 2 XDR-TB patients. In all cases, they died before the end of the first trimester of follow-up.
CONCLUSION: The high frequency of primary pre-extensively drug-resistant tuberculosis underscores the pervasiveness of resistance to anti-tuberculosis drugs and underlines a pressing need for detection of contact cases and early treatment.

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PMID: 39179426 [Indexed for MEDLINE]

80. N-Acyl phenothiazines as mycobacterial ATP synthase inhibitors: Rational design, synthesis and in vitro evaluation against drug sensitive, RR and MDR-TB.

Bioorg Chem. 2024 Oct;151:107702. doi: 10.1016/j.bioorg.2024.107702. Epub 2024 Aug 7.

Reddyrajula R(1), Perveen S(2), Negi A(2), Etikyala U(3), Manga V(3), Sharma R(4), Dalimba UK(5).

Author information:
(1)Central Research Facility, National Institute of Technology Karnataka, Surathkal, Mangalore 575 025, India; Department of Chemical Sciences, National Institute of Pharmaceutical Education and Research (NIPER), Hyderabad 500 037, India.
(2)Infectious Diseases Division, CSIR- Indian Institute of Integrative Medicine, Jammu 180 001, India; Academy of Scientific and Innovative Research (AcSIR), Ghaziabad 201 002, India.
(3)Medicinal Chemistry Laboratory, Department of Chemistry, Osmania University, Hyderabad 500 076, India.

(4)Infectious Diseases Division, CSIR- Indian Institute of Integrative Medicine, Jammu 180 001, India; Academy of Scientific and Innovative Research (AcSIR), Ghaziabad 201 002, India. Electronic address: rashmi.sharma.09@iiim.res.in.
(5)Organic and Materials Chemistry Laboratory, Department of Chemistry, National Institute of Technology Karnataka, Surathkal, Mangalore 575 025, India. Electronic address: udayakumar@nitk.edu.in.

The mycobacterial F-ATP synthase is responsible for the optimal growth, metabolism and viability of Mycobacteria, establishing it as a validated target for the development of anti-TB therapeutics. Herein, we report the discovery of an N-acyl phenothiazine derivative, termed PT6, targeting the mycobacterial F-ATP synthase. PT6 is bactericidal and active against the drug sensitive, Rifampicin-resistant as well as Multidrug-resistant tuberculosis strains. Compound PT6 showed noteworthy inhibition of F-ATP synthesis, exhibiting an IC50 of 0.788 μM in M. smegmatis IMVs and was observed that it could deplete intracellular ATP levels, exhibiting an IC50 of 30 μM. PT6 displayed a high selectivity towards mycobacterial ATP synthase compared to mitochondrial ATP synthase. Compound PT6 showed a minor synergistic effect in combination with Rifampicin and Isoniazid. PT6 demonstrated null cytotoxicity as confirmed by assessing its toxicity against VERO cell lines. Further, the binding mechanism and the activity profile of PT6 were validated by employing in silico techniques such as molecular docking, Prime MM/GBSA, DFT and ADMET analysis. These results suggest that PT6 presents an attractive lead for the discovery of a novel class of mycobacterial F-ATP synthase inhibitors.

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PMID: 39142196 [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.

81. The potential of marine natural Products: Recent Advances in the discovery of Anti-Tuberculosis agents.

Bioorg Chem. 2024 Oct;151:107699. doi: 10.1016/j.bioorg.2024.107699. Epub 2024 Aug 6.

Peng X(1), Zeng Z(1), Hassan S(2), Xue Y(3).

Author information:

(1)School of Pharmaceutical Sciences (Shenzhen), Sun Yat-Sen University, Shenzhen 518107, China.
(2)Institute of Biotechnology and Microbiology, Bacha Khan University, Charsadda 24540, Pakistan.
(3)School of Pharmaceutical Sciences (Shenzhen), Sun Yat-Sen University, Shenzhen 518107, China. Electronic address: xueyb@mail.sysu.edu.cn.

Tuberculosis (TB) is an infectious airborne disease caused by Mycobacterium tuberculosis. Since the 1990 s, many countries have made significant progress in reducing the incidence of TB and associated mortality by improving health services and strengthening surveillance systems. Nevertheless, due to the emergence of multidrug-resistant TB (MDR-TB), alongside extensively drug-resistant TB (XDR-TB) and TB-HIV co-infection, TB remains one of the lead causes of death arising from infectious disease worldwide, especially in developing countries and disadvantaged populations. Marine natural products (MNPs) have received a large amount of attention in recent years as a source of pharmaceutical constituents and lead compounds, and are expected to offer significant resources and potential in the fields of drug development and biotechnology in the years to come. This review summarizes 169 marine natural products and their synthetic derivatives displaying anti-TB activity from 2013 to the present, including their structures, sources and functions. Partial synthetic information and structure-activity relationships (SARs) are also included.

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82. Design and Synthesis of Isatin-Tagged Isoniazid Conjugates with Cogent Antituberculosis and Radical Quenching Competence: In-vitro and In-silico Evaluations.

Chem Biodivers. 2024 Oct;21(10):e202400765. doi: 10.1002/cbdv.202400765. Epub 2024 Sep 6.

Gavadia R(1), Rasgania J(1), Sahu N(1), Varma-Basil M(2), Chauhan V(2)(3), Kumar S(3), Mor S(4), Singh D(1), Jakhar K(1).

Author information:
(1)Department of Chemistry, M. D. University, Rohtak, Haryana, 124001, India.
(2)Department of Microbiology, Vallabhbhai Patel Chest Institute, University of Delhi, Delhi, 110007, India.
(3)Department of Microbiology, M. D. University, Rohtak, Haryana, 124001, India.
(4)Department of Chemistry, Guru Jambheshwar University of Science and Technology, Hisar, Haryana, 125001, India.

In pursuit of potential chemotherapeutic alternates to combat severe tuberculosis infections, novel heterocyclic templates derived from clinically approved anti-TB drug isoniazid and isatin have been synthesized that demonstrate potent inhibitory action against Mycobacterium tuberculosis, and compound 4i with nitrophenyl motif exhibited the highest anti-TB efficacy with a MIC value of 2.54 μM/ml. Notably, the same nitro analog 4i shows the best antioxidant efficacy among all the synthesized compounds with an IC50 value of 37.37 μg/ml, suggesting a synergistic influence of antioxidant proficiency on the anti-TB action. The titled compounds exhibit explicit binding affinity with the InhA receptor. The befitting biochemical reactivity and near-appropriate pharmacokinetic proficiency of the isoniazid conjugates is reflected in the density functional theory (DFT) studies and ADMET screening. The remarkable anti-TB action of the isoniazid cognates with marked radical quenching ability may serve as a base for developing multi-target medications to confront drug-resistant TB pathogens.

DOI: 10.1002/cbdv.202400765
PMID: 39024129 [Indexed for MEDLINE]

83. The Hidden Epidemic of Isoniazid-Resistant Tuberculosis in South Africa.

Ann Am Thorac Soc. 2024 Oct;21(10):1391-1397. doi: 10.1513/AnnalsATS.202312-1076OC.

Klopper M(1)(2)(3), van der Merwe CJ(1)(2)(3)(4), van der Heijden YF(5)(6), Folkerts M(7), Loubser J(1)(2)(3), Streicher EM(1)(2)(3), Mekler K(8), Hayes C(9), Engelthaler DM(7), Metcalfe JZ(10), Warren RM(1)(2)(3).

Author information:
(1)Division of Molecular Biology and Human Genetics, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa.
(2)Department of Science and Innovation, National Research Foundation Centre of Excellence for Biomedical Tuberculosis Research, Cape Town, South Africa.
(3)South African Medical Research Council Centre for Tuberculosis Research, Cape

Town, South Africa.
(4)Centre for Lung Infection and Immunity, Division of Pulmonology, Department of Medicine, University of Cape Town and University of Cape Town Lung Institute, Cape Town, South Africa.
(5)Division of Infectious Diseases, Department of Medicine, School of Medicine, Vanderbilt University, Nashville, Tennessee.
(6)The Aurum Institute, Johannesburg, South Africa.
(7)Pathogen and Microbiome Division, Translational Genomics Research Institute, Flagstaff, Arizona.
(8)Beyond Zero, Port Elizabeth, South Africa.
(9)National Health Laboratory Services, Port Elizabeth, South Africa; and.
(10)Division of Pulmonary and Critical Care Medicine, San Francisco General Hospital and Trauma Center, University of California, San Francisco, San Francisco, California.

Comment in
Ann Am Thorac Soc. 2024 Oct;21(10):1381-1382. doi: 10.1513/AnnalsATS.202407-772ED.

Rationale: Isoniazid-resistant tuberculosis (Hr-TB) is often overlooked in diagnostic algorithms because of reliance on first-line molecular assays testing only for rifampicin resistance. Objectives: To determine the prevalence, outcomes, and molecular mechanisms associated with rifampin-susceptible, isoniazid-resistant TB (Hr-TB) in the Eastern Cape, South Africa. Methods: Between April 2016 and October 2017, sputum samples were collected from patients with rifampin-susceptible TB at baseline and at Weeks 7 and 23 of drug-susceptible TB treatment. We performed isoniazid phenotypic and genotypic drug susceptibility testing, including FluoroTypeMTBDR, Sanger sequencing, targeted next-generation sequencing, and whole-genome sequencing. Results: We analyzed baseline isolates from 766 patients with rifampin-susceptible TB. Of 89 patients (11.7%) who were found to have Hr-TB, 39 (44%) had canonical katG or inhA promoter mutations; 35 (39%) had noncanonical katG mutations (including 5 with underlying large deletions); 4 (5%) had mutations in other candidate genes associated with isoniazid resistance. For 11 (12.4%), no cause of resistance was found. Conclusions: Among patients with rifampin-susceptible TB who were diagnosed using first-line molecular TB assays, there is a high prevalence of Hr-TB. Phenotypic drug susceptibility testing remains the gold standard. To improve the performance of genetic-based phenotyping tests, all isoniazid resistance-associated regions should be included, and such tests should have the ability to identify underlying mutations.

DOI: 10.1513/AnnalsATS.202312-1076OC
PMCID: PMC11451881
PMID: 38935769 [Indexed for MEDLINE]

84. Coarse particulate air pollution and mortality in a multidrug-resistant tuberculosis cohort.

Sci Total Environ. 2024 Oct 10;946:174048. doi: 10.1016/j.scitotenv.2024.174048. Epub 2024 Jun 19.

Feng H(1), Ge E(2), Grubic N(3), Liu X(4), Zhang H(5), Sun Q(6), Wei X(7), Zhou F(8), Huang S(9), Chen Y(8), Guo H(8), Li J(8), Zhang K(10), Luo M(11), Chen L(12).

Author information:
(1)Center for Tuberculosis Control of Guangdong Province, Guangzhou, China. Electronic address: huiyingf08@126.com.
(2)Division of Epidemiology, Dalla Lana School of Public Health, University of Toronto, Canada. Electronic address: erjia.ge@utoronto.ca.
(3)Division of Epidemiology, Dalla Lana School of Public Health, University of Toronto, Canada. Electronic address: nicholas.grubic@utoronto.ca.
(4)School of Spatial Planning and Design, Hangzhou City University, China. Electronic address: liuxin@hzcu.edu.cn.
(5)Guangdong Provincial Key Laboratory of Urbanization and Geo-simulation, School of Geography and Planning, Sun Yat-Sen University, Guangdong Province, China. Electronic address: zhangh573@mail2.sysu.edu.cn.
(6)School of Public Health, Shandong University, China. Electronic address: qiangs@sdu.edu.cn.
(7)Division of Clinic Public Health, Dalla Lana School of Public Health, University of Toronto, Canada. Electronic address: xiaolin.wei@utoronto.ca.
(8)Center for Tuberculosis Control of Guangdong Province, Guangzhou, China.
(9)Center for Tuberculosis Control of Guangdong Province, Guangzhou, China. Electronic address: huangshans@mail2.sysu.edu.cn.
(10)Department of Environmental Health Science, School of Public Health, State University of New York at Albany, Rensselaer, NY 12144, United States. Electronic address: kzhang9@albany.edu.
(11)Guangdong Provincial Key Laboratory of Urbanization and Geo-simulation, School of Geography and Planning, Sun Yat-Sen University, Guangdong Province, China. Electronic address: luom38@mail.sysu.edu.cn.
(12)Guangdong Provincial Institute of Public Health, Guangdong Provincial Center for Disease Control and Prevention, Guangzhou, China. Electronic address: 18928929722@126.com.

RATIONALE: The association between ambient coarse particulate matter (PM2.5-10) and mortality in multi-drug resistant tuberculosis (MDR-TB) patients has not yet been studied. The modifying effects of temperature and humidity on this association are completely unknown.

OBJECTIVES: To evaluate the effects of long-term PM2.5-10 exposures, and their modifications by temperature and humidity on mortality among MDR-TB patients.
METHODS: A Chinese cohort of 3469 MDR-TB patients was followed up from diagnosis until death, loss to follow-up, or the study's end, averaging 2567 days per patient. PM2.5-10 concentrations were derived from the difference between PM10 and PM2.5. Cox proportional hazard models estimated hazard ratios (HRs) per 3.74 μg/m3 (interquartile range, IQR) exposure to PM2.5-10 and all-cause mortality for the full cohort and individuals at distinct long-term and short-term temperature and humidity levels, adjusting for other air pollutants and potential covariates. Exposure-response relationships were quantified using smoothed splines.
RESULTS: Hazard ratios of 1.733 (95% CI, 1.407, 2.135) and 1.427 (1.114, 1.827) were observed for mortality in association with PM2.5-10 exposures for the full cohort under both long-term and short-term exposures to temperature and humidity. Modifying effects by temperature and humidity were heterogenous across sexes, age, treatment history, and surrounding environment measured by greenness and nighttime light levels. Nonlinear exposure-response curves suggestes a cumulative risk of PM2.5-10-related mortality starting from a low exposure concentration around 15 μg/m3.
CONCLUSION: Long-term exposure to PM2.5-10 poses significant harm among MDR-TB patients, with effects modified by temperature and humidity. Immediate surveillance of PM2.5-10 is crucial to mitigate the progression of MDR-TB severity, particularly due to co-exposures to air pollution and adverse weather conditions.

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

85. Actionable mechanisms of drug tolerance and resistance in Mycobacterium tuberculosis.

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Datta D(1)(2), Jamwal S(1), Jyoti N(1), Patnaik S(2), Kumar D(1).

Author information:
(1)Cellular Immunology Group, International Centre for Genetic Engineering and

Biotechnology, New Delhi, India.
(2)School of Biotechnology, Kalinga Institute of Industrial Technology (KIIT), Bhubaneswar, India.

The emergence of antimicrobial resistance (AMR) across bacterial pathogens presents a serious threat to global health. This threat is further exacerbated in tuberculosis (TB), mainly due to a protracted treatment regimen involving a combination of drugs. A diversity of factors contributes to the emergence of drug resistance in TB, which is caused by the pathogen Mycobacterium tuberculosis (Mtb). While the traditional genetic mutation-driven drug resistance mechanisms operate in Mtb, there are also several additional unique features of drug resistance in this pathogen. Research in the past decade has enriched our understanding of such unconventional factors as efflux pumps, bacterial heterogeneity, metabolic states, and host microenvironment. Given that the discovery of new antibiotics is outpaced by the emergence of drug resistance patterns displayed by the pathogen, newer strategies for combating drug resistance are desperately needed. In the context of TB, such approaches include targeting the efflux capability of the pathogen, modulating the host environment to prevent bacterial drug tolerance, and activating the host anti-mycobacterial pathways. In this review, we discuss the traditional mechanisms of drug resistance in Mtb, newer understandings and the shaping of a set of unconventional approaches to target both the emergence and treatment of drug resistance in TB.

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PMID: 38676952 [Indexed for MEDLINE]

86. Drug-resistant tuberculosis: a persistent global health concern.

Nat Rev Microbiol. 2024 Oct;22(10):617-635. doi: 10.1038/s41579-024-01025-1. Epub 2024 Mar 22.

Farhat M(1)(2), Cox H(#)(3), Ghanem M(#)(1), Denkinger CM(4)(5), Rodrigues C(6), Abd El Aziz MS(4), Enkh-Amgalan H(7), Vambe D(8), Ugarte-Gil C(9), Furin J(10), Pai M(11).

Author information:
(1)Department of Biomedical Informatics, Harvard Medical School, Boston, MA, USA.
(2)Division of Pulmonary and Critical Care Medicine, Massachusetts General Hospital, Boston, MA, USA.
(3)Institute of Infectious Disease and Molecular Medicine, Wellcome Centre for

Infectious Disease Research and Division of Medical Microbiology, University of Cape Town, Cape Town, South Africa.
(4)Division of Infectious Disease and Tropical Medicine, Heidelberg University Hospital, Heidelberg, Germany.
(5)German Center for Infection Research (DZIF), partner site Heidelberg University Hospital, Heidelberg, Germany.
(6)P.D. Hinduja Hospital and Medical Research Centre, Mumbai, India.
(7), Ulaanbaatar, Mongolia.
(8)National TB Control Programme, Manzini, Eswatini.
(9)School of Public and Population Health, University of Texas Medical Branch, Galveston, TX, USA.
(10)Department of Global Health and Social Medicine, Harvard Medical School, Boston, MA, USA.
(11)McGill International TB Centre, McGill University, Montreal, Quebec, Canada.
madhukar.pai@mcgill.ca.
(#)Contributed equally

Drug-resistant tuberculosis (TB) is estimated to cause 13% of all antimicrobial resistance-attributable deaths worldwide and is driven by both ongoing resistance acquisition and person-to-person transmission. Poor outcomes are exacerbated by late diagnosis and inadequate access to effective treatment. Advances in rapid molecular testing have recently improved the diagnosis of TB and drug resistance. Next-generation sequencing of Mycobacterium tuberculosis has increased our understanding of genetic resistance mechanisms and can now detect mutations associated with resistance phenotypes. All-oral, shorter drug regimens that can achieve high cure rates of drug-resistant TB within 6-9 months are now available and recommended but have yet to be scaled to global clinical use. Promising regimens for the prevention of drug-resistant TB among high-risk contacts are supported by early clinical trial data but final results are pending. A person-centred approach is crucial in managing drug-resistant TB to reduce the risk of poor treatment outcomes, side effects, stigma and mental health burden associated with the diagnosis. In this Review, we describe current surveillance of drug-resistant TB and the causes, risk factors and determinants of drug resistance as well as the stigma and mental health considerations associated with it. We discuss recent advances in diagnostics and drug-susceptibility testing and outline the progress in developing better treatment and preventive therapies.

DOI: 10.1038/s41579-024-01025-1
PMID: 38519618 [Indexed for MEDLINE]

TB News

1. **Only $1.50 to Detect TB Infection With the Next-Generation SIILTIBCY Test**

https://www.stoptb.org/news/breaking-news-only-150-to-detect-tb-infection-with-next-generation-siiltibcy-test

The SIILTIBCY test is now available worldwide through the STOP TB GDF for $1.50 per dose. This novel testing option provides an alternative to PPD testing and is the first MTB antigen based skin test to be approved and recommended by the Global Fund's Expert Review Panel. This new test has been shown to provide greater specificity in detecting TB in patients who received the BCG vaccine.

2. **John Green to Publish New Nonfiction Book About Tuberculosis: 'Culmination of a Long Journey'**

https://people.com/john-green-new-nonfiction-book-about-tuberculosis-8731962

John Green's new book *Everything is Tuberculosis* is scheduled to be published in Spring 2025. The novel laces the experiences of Henry, a tuberculosis patient Green met through Partner's in Health, with the history and impact of TB.