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1. Update on multidrug-resistant tuberculosis preventive therapy toward the global tuberculosis elimination.

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Matteelli A(1), Lovatti S(2), Rossi B(3), Rossi L(2).

Author information:
(1)Clinic of Infectious and Tropical Diseases, Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy. Electronic address: alberto.matteelli@unibs.it.
(2)Clinic of Infectious and Tropical Diseases, Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy.
(3)Clinic of Infectious and Tropical Diseases, ASST Spedali Civili, Brescia, Italy.

Multidrug-resistant tuberculosis (MDR-TB), the deadliest form of tuberculosis (TB), has been included in the 2024 World Health Organization (WHO) priority list of antibiotic-resistant bacterial pathogens owing to its severe public health implications. Almost two billion people worldwide are infected with Mycobacterium tuberculosis; however, the share of MDR-M.tuberculosis remains uncertain. Mathematical modeling estimates that MDR-TB affects nearly three in every 1000 people worldwide, highlighting the urgent need to address TB preventive treatment (TPT) for contacts of MDR-TB cases. Before 2018, close monitoring of contacts of people with MDR-TB was recommended rather than TPT. However, considering the ethical and public health concerns associated with leaving infected individuals untreated, the WHO updated its guidelines in 2018, 2020, and 2022. Despite the limited evidence at the time, the WHO suggested considering quinolone-based TPT for selected high-risk cases. To close this gap in evidence, two large-scale prospective randomized controlled trials were conducted: VQUIN (VQUIN MDR Australia New Zealand Clinical Trials Registry number, ACTRN12616000215426) and TB-CHAMP (TB-CHAMP ISRCTN Registry number, ISRCTN92634082). Both trials evaluated the efficacy of levofloxacin (Lfx) compared with a placebo for MDR-TB after household exposure in adults and children. A combined meta-analysis of the two trials showed a 60% reduction in TB incidence in the Lfx group, and the difference was statistically significant. Based on these results, in 2024, the WHO recommended the use of 6 months of daily Lfx as a TPT for contacts exposed to MDR/rifampicin-resistant TB. This regimen is cost-effective, safe, demonstrates good efficacy, and does not interact with HIV therapies. Despite these promising results, pre-extensively drug-resistance (XDR)-TB (MDR-TB with documented resistance to quinolones)

remains an emerging concern. Two ongoing trials will address this challenge: the PHOENIx trial (PHOENIx-MDR TB NCT03568383), which will evaluate the efficacy of delamanid compared with isoniazid for preventing M/XDR-TB after household exposure, and the BRANCH-TB trial (NCT0656848), which will assess the efficacy and safety of 1 month of bedaquiline regimen compared with WHO-recommended TPT regimens. Preventing MDR/rifampicin-resistant TB remains a significant challenge for the global elimination of TB. Although the recent WHO recommendation for 6 months of daily Lf is a promising step, expanding the TPT options for pre-XDR TB and addressing drug intolerance are critical. Ongoing and new trials are essential to develop alternative treatment and achieve TB elimination.

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2. Global, regional, and national disease burden of multidrug-resistant tuberculosis without extensive drug resistance, 1990-2021: Findings from the Global Burden of Disease Study 2021.

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Wang X(1), Shang A(2), Chen H(3), Li J(4), Jiang Y(4), Wang L(4), Qiu S(5), Sun F(6), Yue C(7).

Author information:
(1)Department of Clinical Laboratory Medicine, Shanghai Tenth People's Hospital, School of Medicine, Tongji University, Shanghai 200072, PR China.
(2)Department of Laboratory Medicine, The Second People's Hospital of Lianyungang, Clinical College of Xuzhou Medical University, Lianyungang 222006, PR China.
(3)Clinical Research Centre, Zhujiang Hospital, Southern Medical University, Guangzhou, Guangdong 510280, PR China.
(4)Division of TB and HIV/AIDS Prevention, Shanghai Municipal Center for Disease Control and Prevention, Shanghai, PR China.
(5)Department of Clinical Laboratory Medicine, Shanghai Tenth People's Hospital, School of Medicine, Tongji University, Shanghai 200072, PR China. Electronic

address: qsly2022@163.com.
(6)Department of Clinical Laboratory Medicine, Shanghai Tenth People's Hospital, School of Medicine, Tongji University, Shanghai 200072, PR China; Department of Clinical Laboratory, Shanghai Tenth People's Hospital, School of Medicine, School of Chemical Science and Engineering, Tongji University, Shanghai 200072, PR China. Electronic address: sunfenyong@263.net.
(7)Obstetrics & Gynecology Hospital of Fudan University, Shanghai Key Lab of Reproduction and Development, Shanghai Key Lab of Female Reproductive Endocrine Related Diseases, Shanghai, PR China. Electronic address: 20111250007@fudan.edu.cn.

OBJECTIVE: Utilizing Global Burden of Disease Study (GBD 2021) data, this study aims to illustrate trends and spatiotemporal patterns of multidrug-resistant tuberculosis (MDR-TB) burden from 1990 to 2021, and explore their potential mechanisms.
METHODS: This research extracted core indicators including incidence, mortality, prevalence, and disability-adjusted life years (DALYs), with their age-standardized rate (ASR). Joinpoint regression, age-period-cohort analysis, inequality analysis, and frontier analysis were applied to describe the temporal and spatial trends of the disease burden. Decomposition analysis and risk factor analysis were performed to explore factors associated with MDR-TB burden fluctuation. Bayesian Age-Period-Cohort (BAPC) model was used to project the disease burden till 2050.
RESULTS: Global MDR-TB cases and ASRs of all indicators rose from 1990 to 2021, with heavier burden in older populations and lower socioeconomic regions. Cross-country inequality widened over time. Frontier analysis identified countries including India and Russia with considerable potential for improvement in disease control. Decomposition analysis uncovered epidemiological changes as the main driver of the growing burden globally. Risk factors of MDR-TB in different regions and age groups were heterogeneous. The numbers and ASRs of all indicators are predicted to increase by 2050.
CONCLUSIONS: This study revealed that the global disease burden of MDR-TB increased from 1990 to 2021 and is predicted to grow till 2050. Disparities among different social-demographic regions were remarkable and extended over time. Epidemiological changes contributed most to the escalated disease burden. Targeted public health strategies should be adopted for patients in specific regions and age groups.

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declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

3. A Call to Action: Empowering Pharmacists in Drug-Resistant Tuberculosis Management.

J Multidiscip Healthc. 2025 Jun 17;18:3531-3544. doi: 10.2147/JMDH.S517965. eCollection 2025.

Alfaqeeh M(1)(2), Santoso P(3), Alffenaar JW(4)(5), Pradipta IS(2)(6)(7).

Author information:
(1)Doctoral Program of Pharmacy, Faculty of Pharmacy, Universitas Padjadjaran, Bandung, Indonesia.
(2)Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, Universitas Padjadjaran, Bandung, Indonesia.
(3)Division of Respirology and Critical Care, Department of Internal Medicine Dr. Hasan Sadikin General Hospital /Faculty of Medicine, Universitas Padjadjaran, Bandung, Indonesia.
(4)School of Pharmacy, Faculty of Medicine and Health, University of Sydney, Sydney, Australia.
(5)Sydney Infectious Diseases Institute, University of Sydney, Sydney, Australia.
(6)Center of Excellence for Pharmaceutical Care Innovation, Universitas Padjadjaran, Bandung, Indonesia.
(7)Indonesian Tuberculosis Research Network/Jetset TB, Jakarta, Indonesia.

Drug-resistant tuberculosis (DR-TB) continues to be a major global health threat, and while advancements in drug therapies have been made, the role of pharmacists in improving patient outcomes has not been fully optimized. This review aims to describe the types, resistance mechanisms, and management strategies of DR-TB, with a focus on discussing the critical role of pharmacists in optimizing treatment outcomes for DR-TB patients. A narrative review approach was adopted to provide an updated and evidence-based perspective. Additionally, manual review of reference lists from the retrieved articles was performed to identify additional relevant studies. The review identifies types of DR-TB, including mono-, poly-, rifampicin-, multi-, pre-extensively, and extensively-drug resistance. Resistance mechanisms are outlined, highlighting mutations in key genes, such as those involved in rifampicin and isoniazid (INH) resistance, which compromise treatment efficacy. The treatment regimens for DR-TB include the INH-R regimen, Bedaquiline, Pretomanid, and Linezolid (with or without Moxifloxacin) (BPaL(M) regimen, shorter oral regimen, and longer oral

regimen, each tailored to the specific resistance pattern and patient condition. The challenges in managing DR-TB include complex treatment regimens and side effects, social barriers such as stigma and adherence issues, and system-related obstacles like limited resources and healthcare infrastructure. The review underscores pharmacists' vital yet underutilized role in addressing challenges. Pharmacists' contributions include patient counseling to improve adherence, and optimizing regimens for vulnerable populations and therapeutic drug monitoring. Addressing DR-TB requires a multifaceted approach, with pharmacists playing a critical role in its management. Their contributions are key to improving patient outcomes and overcoming the challenges associated with DR-TB management.

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4. Targeted next-generation sequencing - a promising approach in the diagnosis of Mycobacterium tuberculosis and drug resistance.

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Wu X(#)(1)(2), Tan G(#)(3), Sun C(#)(4), Wang Y(5), Yang J(1), Wu C(5), Hu C(6), Yu F(7)(8).

Author information:
(1)Department of Clinical Laboratory, Shanghai Pulmonary Hospital, School of Medicine, Tongji University, Shanghai, China.
(2)Shanghai Key Laboratory of Tuberculosis, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai, China.
(3)Department of Clinical Laboratory, Shanghai University of Traditional Chinese Medical Attached Shuguang Hospital, Shanghai, China.
(4)Department of Clinical Laboratory, Shanghai Eye Disease Prevention & Treatment Center, Shanghai Eye Hospital, Shanghai, China.
(5)Guangzhou KingCreate Biotechnology Co., Ltd., Guangzhou, China.
(6)Guangzhou KingCreate Biotechnology Co., Ltd., Guangzhou, China. huzh@kingcreate.com.cn.
(7)Department of Clinical Laboratory, Shanghai Pulmonary Hospital, School of Medicine, Tongji University, Shanghai, China. wzjxyfy@163.com.

(8)Department of Laboratory Medicine, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, 325015, China. wzjxyfy@163.com.
(#)Contributed equally

Targeted next-generation sequencing (tNGS) offers a high-throughput, culture-independent approach that delivers a comprehensive resistance profile in a significantly shorter turn-around time, making it promising in enhancing tuberculosis (TB) diagnosis and informing treatment decisions. This study aims to evaluate the performance of tNGS in the TB diagnosis and drug resistance detection of Mycobacterium tuberculosis (MTB) using MTB clinical isolates and bronchoalveolar lavage fluid (BALF) samples. A total of 143 MTB clinical isolates were assessed, tNGS, phenotypic antimicrobial susceptibility testing (AST), and AST based on whole genome sequencing (WGS) exhibited high concordance rates, averaging 95.10% and 97.05%. Among 158 BALF samples, culture, Xpert MTB/RIF, and tNGS reported 29, 70 and 111 positives, respectively. In the confirmed cases with etiological evidence (smears, cultures, or molecular test), the positive rate of tNGS (73/83, 87.95%) was higher than that of Xpert MTB (67/83, 80.72%). Additionally, 45% (27/60) of clinically diagnosed cases (with imaging or immunological evidence) were positive for tNGS. Further validation on the discrepant results between tNGS and Xpert MTB/RIF with droplet digital PCR (ddPCR) yielded 35 positives, tNGS detected all, and Xpert MTB/RIF only identified 6 positives. In conclusion, tNGS demonstrates robust and rapid performance in the identification of MTB and its associated drug resistance, and can be directly applied to clinical samples, positioning it as a promising approach for laboratory testing of tuberculosis.

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5. Unravelling the transcriptome of the human tuberculosis lesion and its clinical implications.

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Fonseca KL(1)(2), Lozano JJ(3)(4), Despuig A(1)(2), Habgood-Coote D(5), Sidorova J(3)(4), Aznar D(1)(6), Arias L(1)(2), Del Río-Álvarez Á(7)(8)(9), Carrillo-Reixach J(7)(8)(9), Goff A(10), Wildner LM(10), Gogishvili S(11), Nikolaishvili K(11), Shubladze N(11), Avaliani Z(11)(12), Tapia G(13)(14), Rodríguez-Martínez P(13)(14), Cardona PJ(1)(2)(6)(15), Martinón-Torres F(2)(16)(17)(18), Salas A(2)(18)(19)(20), Gómez-Carballa A(2)(18)(19)(20), Armengol C(7)(8)(9), Waddell SJ(10), Kaforou M(5)(21), O'Garra A(22)(23), Vashakidze S(11)(24), Vilaplana C(25)(26)(27)(28).

Author information:
(1)Experimental Tuberculosis Unit (UTE), Fundació Institut Germans Trias i Pujol (IGTP), Badalona, Spain.
(2)Centro de Investigación Biomédica en Red de Enfermedades Respiratorias (CIBERES), Madrid, Spain.
(3)Bioinformatic Platform, Centro de Investigación Biomédica en Red de Enfermedades Hepática y Digestivas (CIBERehd), Barcelona, Spain.
(4)Hospital Clínic de Barcelona, Barcelona, Spain.
(5)Department of Infectious Diseases, Imperial College London, London, UK.
(6)Department of Genetics and Microbiology, Universitat Autònoma de Barcelona (UAB), Bellaterra, Spain.
(7)Childhood Liver Oncology Group, Germans Trias i Pujol Research Institute (IGTP), Badalona, Spain.
(8)Translational Program in Cancer Research (CARE), Germans Trias i Pujol Research Institute (IGTP), Badalona, Spain.
(9)Liver and Digestive Diseases Networking Biomedical Research Centre (CIBER), Madrid, Spain.
(10)Global Health and Infection, Brighton and Sussex Medical School, University of Sussex, Brighton, UK.
(11)National Center for Tuberculosis and Lung Diseases (NCTLD), Tbilisi, Georgia.
(12)European University, Tbilisi, Georgia.
(13)Pathology Department, Hospital Germans Trias i Pujol, Badalona, Spain.
(14)Universitat Autònoma de Barcelona, Barcelona, Spain.
(15)Microbiology Department, Northern Metropolitan Clinical Laboratory, Hospital Universitari Germans Trias i Pujol, Badalona, Spain.
(16)Genetics, Vaccines and Pediatric Infectious Diseases Research Group (GENVIP), Instituto de Investigación Sanitaria de Santiago (IDIS), Santiago de Compostela, Spain.
(17)Universidad de Santiago de Compostela (USC), Santiago de Compostela, Spain.
(18)Translational Pediatrics and Infectious Diseases, Hospital Clínico Universitario de Santiago de Compostela (SERGAS), Santiago de Compostela, Spain.
(19)Unidade de Xenética, Instituto de Ciencias Forenses (INCIFOR), Universidade de Santiago de Compostela, Santiago de Compostela, Spain.

(20)GenPoB Research Group, Instituto de Investigación Sanitaria (IDIS), Santiago de Compostela, Spain.
(21)Centre for Paediatrics and Child Health, Imperial College London, London, UK.
(22)Immunoregulation and Infection Laboratory, The Francis Crick Institute, London, UK.
(23)National Heart and Lung Institute, Imperial College, London, UK.
(24)The University of Georgia, Tbilisi, Georgia.
(25)Experimental Tuberculosis Unit (UTE), Fundació Institut Germans Trias i Pujol (IGTP), Badalona, Spain. cvilaplana@igtp.cat.
(26)Centro de Investigación Biomédica en Red de Enfermedades Respiratorias (CIBERES), Madrid, Spain. cvilaplana@igtp.cat.
(27)Department of Genetics and Microbiology, Universitat Autònoma de Barcelona (UAB), Bellaterra, Spain. cvilaplana@igtp.cat.
(28)Microbiology Department, Northern Metropolitan Clinical Laboratory, Hospital Universitari Germans Trias i Pujol, Badalona, Spain. cvilaplana@igtp.cat.

The tuberculosis (TB) lesion is a complex structure, contributing to the overall spectrum of TB. We characterise, using RNA sequencing, 44 fresh human pulmonary TB lesion samples from 13 TB individuals (drug-sensitive and multidrug-resistant TB) undergoing therapeutic surgery. We confirm clear separation between the TB lesion and adjacent non-lesional tissue, with the lesion samples consistently displaying increased inflammatory profile despite heterogeneity. Using weighted correlation network analysis, we identify 17 transcriptional modules associated with TB lesion and demonstrate a gradient of immune-related transcript abundance according to spatial organization of the lesion. Furthermore, we associate the modular transcriptional signature of the TB lesion with clinical surrogates of treatment efficacy and TB severity. We show that patients with worse disease present an overabundance of immune/inflammation-related modules and downregulated tissue repair and metabolism modules. Our findings provide evidence of a relationship between clinical parameters, treatment response and immune signatures at the infection site.

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manuscript. The remaining authors declare no competing interests.

6. Nutritional Deficiencies and Management in Tuberculosis: Pharmacotherapeutic and Clinical Implications.

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Fâcă AI(1)(2), Udeanu DI(1)(2), Arsene AL(1)(2), Mahler B(2)(3), Drăgănescu D(1), Apetroaei MM(1).

Author information:
(1)Faculty of Pharmacy, Carol Davila University of Medicine and Pharmacy, 6, Traian Vuia Street, 020956 Bucharest, Romania.
(2)Marius Nasta Institute of Pneumology, 90, Viilor Street, 050159 Bucharest, Romania.
(3)Faculty of Medicine, Carol Davila University of Medicine and Pharmacy, 8, Eroii Sanitari Street, 050474 Bucharest, Romania.

Tuberculosis is an infectious condition caused by Mycobacterium tuberculosis, primarily targeting the pulmonary system, with the potential to disseminate to various other organs via the haematogenous pathway, ranking among the top ten causes of global mortality. Tuberculosis remains a serious public health problem worldwide. This narrative review aims to emphasise the clinical importance of the inter-relationships between nutrition, pharmacotherapy, and the most common drug-nutrient interactions in the context of tuberculosis and multi-drug-resistant tuberculosis management. Nowadays, pharmacologic approaches utilise polytherapeutic regimens that, although showing increased efficacy, prominently affect the nutritional status of patients and modify multiple metabolic pathways, thus influencing both the effectiveness of therapy and the patient outcomes. There is much evidence that antituberculosis drugs are associated with deficiencies in essential vitamins and various micronutrients, leading to serious adverse consequences. Moreover, poor nutrition exacerbates TB outcomes, and TB further exacerbates nutritional status, a vicious cycle that is particularly prevalent in low-resource environments. Nutritional support is necessary, and clinicians ought to evaluate it on a patient-by-patient basis, as empirical evidence has shown that it can improve immune recovery, decrease tuberculosis-associated morbidity, and increase adherence to therapy. However, drug-food interactions are increasingly prevalent, and patients with tuberculosis require personalised dietary and pharmacological regimens. In this context, antituberculosis treatment requires a holistic approach, based on the collaboration of the prescribing physician, pharmacist, and nutritionist, to assess the patient's needs from a nutritional and pharmacological perspective, with the ultimate goal of decreasing mortality and improving the prognosis of

patients through personalised therapies.

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7. Isoniazid-resistant TB and associated factors in Ethiopia.

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Moga S(1)(2), Abebe T(1), Bobosha K(3), Alemu A(2), Diriba G(2), Harrington KRV(4), Lyles RH(5), Blumberg HM(6)(7), Kempker RR(7).

Author information:
(1)Addis Ababa University (AAU), Department of Microbiology, Immunology, and Parasitology, School of Medicine, College of Health Sciences, Addis Ababa, Ethiopia.
(2)Ethiopian Public Health Institute (EPHI), Infectious Diseases Research Directorate, Addis Ababa, Ethiopia.
(3)Armauer Hansen Research Institute (AHRI), Mycobacterial Diseases Research Directorate, Addis Ababa, Ethiopia.
(4)Emory University Rollins School of Public Health, Department of Epidemiology, Atlanta, GA, USA.
(5)Emory University Rollins School of Public Health, Department of Biostatistics and Bioinformatics, Atlanta, GA, USA.
(6)Emory University Rollins School of Public Health, Departments of Epidemiology and Global Health, Atlanta, GA, USA.
(7)Emory University School of Medicine, Department of Medicine, Division of Infectious Diseases, Atlanta, GA, USA.

BACKGROUND: Isoniazid-resistant, rifampicin-susceptible Mycobacterium tuberculosis (Hr-TB) is the most common form of drug-resistant TB (DR-TB). We investigated the prevalence of and risk factors for Hr-TB in Ethiopia.
METHODS: A cross-sectional study was conducted to determine the magnitude of Hr-TB, and to compare characteristics of persons with Hr-TB to those with multidrug-resistant TB (MDR-TB) and INH/RMP-susceptible TB identified during the National Drug Resistance Survey from 2017-2019.
RESULTS: Among 1927 M. tuberculosis isolates recovered from persons with pulmonary TB, the prevalence of Hr-TB was 4.1% (95% CI 3.2-5.1), whereas the prevalence of MDR-TB was 1.9%. (95% CI 1.3-2.6). Unlike MDR-TB, the occurrence

of Hr-TB did not differ significantly between new and previously treated TB cases (P = 0.67). The prevalence of Hr-TB cases was high in the Amhara (8.0%, 95% CI 4.8-12.5) region and Addis Ababa (7.1%, 95% CI 3.4-13.0). The proportion of Hr-TB increased with age (OR 1.02, 95% CI 1.01-1.04; P = 0.035). Compared to INH/RMP-susceptible TB, Hr-TB was more likely to harbor resistance to ethambutol, streptomycin and pyrazinamide (P < 0.0001).
CONCLUSIONS: Hr-TB is the most prevalent type of DR-TB in Ethiopia and varies among regional states. Given the lack of identifiable clinical factors associated with Hr-TB, we recommend screening all bacteriologically confirmed TB cases for INH resistance at baseline.

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

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

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

Cycloserine (CS) is a widely used drug for drug-resistant tuberculosis (DR-TB) treatment. The World Health Organization (WHO) recently suggested a critical concentration (CC) for CS using the MGIT 960 system (MGIT). To strengthen our DR-TB management program, we performed CS resistance analyses to provide comprehensive drug susceptibility testing (DST). This retrospective study included Mycobacterium tuberculosis complex (MTBC) isolates obtained from 114 rifampin-resistant (RR) and multidrug-resistant (MDR) TB cases. We compared the results of phenotypic DST (pDST) and genotypic DST (gDST) and evaluated the minimum inhibitory concentration (MIC) using both MGIT and the Sensititre MYCOTB MIC Plate (Sensititre). Sanger sequencing and whole-genome sequencing were conducted to analyze the mutations of CS-resistant-associated ald and alr genes. Our results indicated that the optimal consistency with gDST was achieved with

the CC of 16 µg/mL for MGIT, which aligns with the WHO recommendations, and the CC of 8 µg/mL for Sensititre. Of the 114 MTBC isolates, we found 5 (4.4%) CS-MGIT-resistant isolates, which all harbored mutations in the alr gene, including three previously known mutations M343T, T20M, L113R, and a novel mutation R243S, whereas seven low-MIC isolates harboring alr Q30R mutations might not be associated with CS resistance. Notably, M1I, E118K, and A184T in the ald gene and L113R, R243S, S261N, and M343T in the alr gene were predicted to have a destabilizing effect, which could interfere with protein functions and induce drug resistance. For accurate routine diagnosis of CS susceptibility, we adopted the CC of 16 µg/mL and suggested an interim 8 µg/mL using MGIT and Sensititre, respectively.IMPORTANCETo strengthen the DR-TB management program in Taiwan, we performed cycloserine (CS) resistance analyses to enhance treatment outcomes. Of the 114 drug-resistant tuberculosis (DR-TB) isolates, we found 5 (4.4%) CS-MGIT-resistant isolates, with four isolates classified as multidrug-resistant (MDR)-TB and one isolate as Pre-XDR-TB. In addition, we observed all CS-MGIT-resistant isolates harbored mutations in the alr gene, including three previously known high-confidence mutations M343T, T20M, and L113R, as well as the novel R243S mutation. We also found that mutations could lead to CS resistance by disrupting protein stability.

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

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

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

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

BACKGROUND: Tongue swabs have emerged as a promising non-invasive alternative for TB diagnosis. This study aimed to evaluate the diagnostic performance of tongue swab-based assays for detecting Mycobacterium tuberculosis (MTB) and anti-TB drug resistance.
METHODS: We conducted a multicenter study in five TB-designated hospitals in China from May to August 2024. Tongue swabs and sputum samples were collected from 720 adults with symptoms suggestive of pulmonary TB. PCR-based tongue swab testing targeting MTB-specific sequences was evaluated against microbiological reference standards (MRS) and Xpert MTB/RIF. Tongue swab-based targeted next generation sequencing was conducted to diagnose the drug-resistant TB.
RESULTS: Tongue swab testing demonstrated high diagnostic accuracy, with a concordance rate of 95.1% (95% CI: 93.2-96.5) compared to Xpert MTB/RIF, and with a sensitivity of 88.6% (95% CI: 85.3-91.8) and specificity of 98.3% (95% CI: 97.0-99.7) compared to MRS. Tongue swabs supported the detection of drug-resistant MTB using targeted next-generation sequencing, with detection rates of 98.66% for Ct <30, 91.53% for Ct 30-33, and 84.62% for Ct 33-34, declining sharply to 57.14% for Ct 34-35.
CONCLUSION: PCR-based tongue swab testing offers a rapid, non-invasive

alternative for TB diagnosis with high accuracy, particularly in paucibacillary cases or individuals unable to provide sputum. Although all participants in this study were able to provide sputum, tongue swabs may offer an alternative in situations where sputum collection is challenging. Further optimization of sampling and molecular techniques is essential to improve reliability and support broader implementation. Integrating tongue swab diagnostics with existing TB control programs could enhance the detection accuracy, improve drug resistance monitoring and reduce transmissions.

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Conflict of interest statement: Declaration of Competing Interest The materials, reagents, and instruments used in this study were provided by Hangzhou DIAN Medical Laboratory Center Co., Ltd. The authors have no financial interests or conflicts of interest with any organization or entity, except for those related to the topics or materials discussed in the manuscript. The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

10. Operational considerations of select new treatment recommendations for drug-susceptible and drug-resistant tuberculosis.

J Clin Tuberc Other Mycobact Dis. 2025 May 24;40:100536. doi: 10.1016/j.jctube.2025.100536. eCollection 2025 Aug.

Wilson JW(1), Temesgen Z(1), Gaensbauer JT(2).

Author information:
(1)Division of Public Health, Infectious Diseases, Occupational Medicine, Section of Infectious Diseases, Mayo Clinic College of Medicine, USA.
(2)Division of Pediatric Infectious Diseases, Mayo Clinic College of Medicine, USA.

A number of management updates recently have been published for both drug-susceptible and drug-resistant tuberculosis (TB), TB in children, and contacts of patients with drug-resistant TB. The operationalization and application of these recommendations, which reflect favorable clinical trial outcomes, may vary significantly for different patient groups and in different settings. Defining the best treatment approach for each patient requires the integration of multiple data points including organism culture growth and

corresponding drug susceptibility profiles, specific TB syndrome, concurrent patient co-morbidities and available public health resources. We review several updated TB treatment recommendations and discuss applicable strengths, select limitations and corresponding precautions as they pertain to diverging patient groups, TB syndromes, and public health capacity.

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PMID: 40520337

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

11.Genomic characterization of multidrug-resistant tuberculosis in Shanghai, China: antibiotic resistance, virulence and transmission.

JAC Antimicrob Resist. 2025 May 8;7(3):dlaf064. doi: 10.1093/jacamr/dlaf064. eCollection 2025 Jun.

Guo Y(1)(2), Lu J(3), Jin P(4), Qiu Z(5), Yu F(6), Zhu Y(7), Huang J(1).

Author information:
(1)School of Medicine, Shenzhen Campus of Sun Yat-Sen University, Shenzhen, Guangdong 518107, China.
(2)State Key Laboratory of Respiratory Disease, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, Guangdong 510120, China.
(3)Institute of Infectious Disease, The Second Affiliated Hospital of Tianjin Medical University, Tianjin 300222, China.
(4)Department of Laboratory Medicine, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 201801, China.
(5)Independent Researcher, Shenzhen, Guangdong 518000, China.
(6)Department of Laboratory Medicine, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai 200433, China.
(7)Systems Biology Center, Tianjin Institute of Industrial Biotechnology, Chinese Academy of Sciences, Tianjin 300308, China.

OBJECTIVES: Whole-genome sequencing (WGS) was employed to investigate antibiotic resistance, virulence and transmission profiles of multidrug-resistant tuberculosis (MDR-TB) isolates from Shanghai, China.
METHODS: A total of 306 MDR-TB clinical isolates were collected from Shanghai

Pulmonary Hospital and underwent phenotypic drug susceptibility testing (DST) for common anti-TB drugs and WGS. Combined 778 published bacterial sequences, we performed phylogenetic analysis, resistance and virulence gene identification to understand the genetic relationships and resistance mechanisms among those strains.
RESULTS: WGS determination, supported by DST, revealed high resistance rates for isoniazid (83.66%) and rifampicin (90.20%) among the MDR-TB isolates. Key resistance-associated mutations included katG Ser315Thr for isoniazid, rpoB mutations for rifampicin, and embB Met306Val for ethambutol. WGS demonstrated >90% concordance with culture-based DST for most drugs, except ethambutol that showed a 76.80% concordance. Analyses of virulence factors and phylogenetics revealed the genetically homogeneous, endemic MDR-TB population in Shanghai, with no evidence of recent transmission.
CONCLUSIONS: This study highlights the genetic homogeneity and endemic nature of MDR-TB in Shanghai, providing insights into key resistance mechanisms of TB.

DOI: 10.1093/jacamr/dlaf064
PMCID: PMC12059630
PMID: 40342723

12. Prevalence and molecular characterization of drug-resistant Mycobacterium tuberculosis in Heyuan City in China.

Front Cell Infect Microbiol. 2025 Jun 12;15:1586938. doi: 10.3389/fcimb.2025.1586938. eCollection 2025.

Qiu D(1)(2), Ma J(3), Liu Z(4), Zeng X(1).

Author information:
(1)Medical Laboratory, Heyuan Key Laboratory of Molecular Diagnosis and Disease Prevention and Treatment, Doctors Station of Guangdong Province, Heyuan People's Hospital, Heyuan, Guangdong, China.
(2)Department of Traditional Chinese Medicine, Heyuan People's Hospital, Heyuan, Guangdong, China.
(3)Department of Clinical Laboratory, Heyuan People's Hospital, Heyuan, Guangdong, China.
(4)Department of Integrated Enforcement, Heyuan Health Supervision Institute, Heyuan, Guangdong, China.

PURPOSE: Tuberculosis (TB) represents a significant global public health

challenge, with China identified as a high-burden country. Data on the prevalence of drug resistance is crucial for informing the selection of appropriate pharmacological interventions for the treatment of drug-resistant tuberculosis (DR-TB).To evaluate the prevalence and drug resistance patterns among patients with DR-TB in Heyuan City, China.
METHODS: All 291 patients registered between April 2021 and March 2023 were tested for drug resistance, and information about their medical history and demographics was collected directly from the hospital's computer database. Eight genes were analyzed for mutations associated with resistance to five antituberculosis drugs: the katG, ahpC, and inhA promoters for isoniazid (INH); rpoB for rifampicin (RIF); embB for ethambutol (EMB); gyrA for fluoroquinolones (FQs); and rrs and rpsL for streptomycin (STR). All strains were genotyped using fluorescence melting curve analysis.
RESULTS: In Heyuan, 24.4% (71/291) of patients with treatment-resistant TB were resistant to at least one drug. Following are the rates of general resistance to each drug: RIF (28/272, 10.29%), INH (38/274, 13.87%), FQs (10/259, 3.86%), EMB (20/248, 8.06%), and STR (15/150, 10.00%). Age or gender had no statistically significant impact on the likelihood of developing drug resistance. Nevertheless, a statistically significant difference was observed between the three strategies of drug resistance testing, AFB testing, and MTB antibody testing. There were 48 cases of single-drug resistance and 23 cases of multiple-drug resistance among the 71 drug-resistant patients. Eight genes had 127 altered nucleotide sequences, with KatG315 (20.47%) having the most significant incidence of mutations. The top three mutated genes were rpoB (32.28%), katG (23.62%), and embB (15.75%).
CONCLUSION: These findings may be helpful in Heyuan City for the quick molecular identification of DR-TB isolates in clinical samples.

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PMCID: PMC12198221
PMID: 40575484 [Indexed for MEDLINE]

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

13. Pharmacokinetics and Safety of Clofazimine in Children With Rifampicin-Resistant Tuberculosis.

J Infect Dis. 2025 Jun 2;231(5):e873-e881. doi: 10.1093/infdis/jiaf057.

Hughes JA(1), Solans BP(2)(3), Garcia-Prats AJ(1)(4), Draper HR(1), Schaaf HS(1), Nielsen JC(5), Nortier E(1), Courtney I(1), Palmer M(1), van der Laan L(1), Savic RM(2)(3), Hesseling AC(1).

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 Bioengineering and Therapeutic Sciences, Schools of Pharmacy and Medicine.
(3)UCSF Center for Tuberculosis, University of California San Francisco.
(4)Department of Pediatrics, School of Medicine and Public Health, University of Wisconsin, Madison.
(5)Department of Pediatrics, Hassenfeld Children's Hospital at NYU Langone, New York, New York.

BACKGROUND: We described the pharmacokinetics and safety of clofazimine in children treated for multidrug/rifampicin-resistant tuberculosis (MDR/RR-TB).
METHODS: Children aged <18 years were eligible. Clofazimine was administered by weight-based dosing. Sparse and semi-intensive pharmacokinetic sampling was completed at baseline and weeks 2 and 16. Clofazimine weekly area under the concentration time-curve (wAUC) was compared with the target wAUC (60.87 mg × h/L and 111.79 mg × h/L) in adults receiving clofazimine (100 mg) daily for MDR/RR-TB and leprosy, respectively. Safety monitoring included measurement of QT interval prolongation and laboratory assessment.
RESULTS: Twenty children were included: median age was 6.0 years (IQR, 1.6-14.4); 6 (30%) were male. Median clofazimine wAUC was 162.94 (IQR, 130.06-263.95), >25% higher than the target adult wAUC in adults with MDR/RR-TB (111.79; IQR, 81.9-151.9). No serious or grade ≥3 cardiac events occurred. There was a QT interval increase of 0.02 milliseconds for every 1-µg/L increase in clofazimine concentration. One severe adverse event (elevated alanine transferase) led to temporary withdrawal of clofazimine.
CONCLUSIONS: The clofazimine doses used achieved substantially higher exposures in children than adults receiving standard clofazimine doses. The association of higher clofazimine exposures and QT interval prolongation may pose unnecessary risk to children, particularly in combination with other QT-prolonging drugs.
CLINICAL TRIALS REGISTRATION: South African National Clinical Trials Register (https://sanctr.samrc.ac.za/; DOH-27-0620-6415).

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PMCID: PMC12128054

PMID: 39932891 [Indexed for MEDLINE]

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14. Strengthening TB laboratory systems: addressing diagnostic and systemic barriers in drug-resistant TB.

Public Health Action. 2025 Jun 4;15(2):88-90. doi: 10.5588/pha.25.0009. eCollection 2025 Jun.

Jung JK(1), Quelapio M(2)(3), Cho SN(1).

Author information:
(1)International Tuberculosis Research Center, 236 Gaposunhwan-ro, Masanhappo-gu, Changwon-si, Gyeongsangnam-do, Republic of Korea.
(2)KNCV TB Foundation, Postbus 146, 2501 CC Den Haag, The Hague, The Netherlands.
(3)TB Alliance, 40 Wall Street, 24th Floor, New York, USA.

As part of the LIFT-TB project, we investigated the efficacy and safety of the BPaL regimen, while enhancing laboratory diagnostic capacity for drug-resistant-TB. Challenges include sample contamination, excessive workload, test kit shortages, unreliable results and systemic issues such as infrastructure, delayed procurement, workforce constraints and reliance on paper-based data reporting. Our study highlights the need for a system-level approach backed by strong national leadership to strengthen TB diagnostic capacity. Although countries must take ownership of laboratory system improvements, a harmonized and coordinated approach among international stakeholders is essential in specialized areas, such as external quality assurance, capacity building, and introducing innovative diagnostic technologies.

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PMID: 40487466

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

15. Spatiotemporal analysis of tuberculosis drug resistance and associated risk factors in Tanzania.

Ther Adv Infect Dis. 2025 Jun 1;12:20499361251339576. doi: 10.1177/20499361251339576. eCollection 2025 Jan-Dec.

Bwire BW(1), Mbago MCY(2), Msengwa AS(2)(3).

Author information:
(1)Department of Statistics, University of Dar es Salaam, P.O. Box 35047, Dar es Salaam 14115, Tanzania.
(2)Department of Statistics, University of Dar es Salaam, Dar es Salaam, Tanzania.
(3)National Bureau of Statistics, Dodoma, Tanzania.

BACKGROUND: The prevalence of tuberculosis (TB) multi-drug resistance is increasing worldwide, including in Tanzania. This trend hinders the attainment of sustainable development goal number three as it increases the number of cases of the disease and treatment costs. Fewer cases of drug resistance have been reported over time, making it necessary to demand models that can handle an excessive number of zero counts. This study employed the zero-inflated Poisson (ZIP) models suitable for such data to assess drug resistance patterns.
OBJECTIVE: To examine the TB drug resistance spatiotemporal risk patterns and associated risk factors using health facility case notification data.
DESIGN: A retrospective cohort study utilizing TB drug resistance case notification data from the District Health Information System 2 for Tanzania Mainland between 2018 and 2020.
METHODS: The study was conducted in Tanzania Mainland and utilized TB drug resistance case data from 184 councils. Six hundred fifty-two (652) TB drug resistance cases were analyzed using the Bayesian ZIP spatiotemporal model to identify high-risk areas and risk factors for TB drug resistance. The deviance information criterion guided model selection.
RESULTS: The findings revealed a higher prevalence of drug resistance among males (65.2%), individuals aged 35-49 years (33.7%), persons living without HIV (66.4%) and new TB cases (70.7%). Spatiotemporal modelling indicated significant relationships between drug resistance and sex, age, TB treatment history and HIV status. Males were 1.4 times more likely to develop drug resistance than females. Children aged 0-4 and 5-14 years were 25 and 8.3 times less likely to develop drug resistance than adults aged 35-49. Persons living with HIV and those with unknown HIV status were 1.2 and 3.4 times less likely to develop drug resistance, respectively, than persons living without HIV. Individuals with a previous TB treatment history were three times more likely to develop drug resistance compared to new cases.

CONCLUSION: The Bayesian ZIP spatiotemporal models provide critical insights by identifying high-risk populations and areas, enabling targeted interventions to control multi-drug resistant TB. The study further concludes that resistance to anti-TB drugs is highly associated with sex, age and previous treatment history. To mitigate its spread and impact, the study recommends strengthening awareness campaigns on adherence to treatment guidelines and understanding the risk factors associated with TB drug resistance.

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PMCID: PMC12130660
PMID: 40463415

16. Multimodal radiomics integrating deep learning and clinical features for diagnosing multidrug-resistant tuberculosis in HIV/AIDS patients.

J Glob Antimicrob Resist. 2025 Jun;43:134-142. doi: 10.1016/j.jgar.2025.04.013. Epub 2025 May 3.

Song C(1), Huang A(2), Zhao C(1), Wen L(2), Song S(3), Lin Y(2), Xu C(2), Qiang H(2), Zhu Q(4).

Author information:
(1)Department of Tuberculosis, The Fourth People's Hospital of Nanning, Nanning, Guangxi, China; Guangxi Medical University, Nanning, Guangxi, China.
(2)Department of Tuberculosis, The Fourth People's Hospital of Nanning, Nanning, Guangxi, China.
(3)Department of Radiology, The Fourth People's Hospital of Nanning, Nanning, Guangxi, China.
(4)Department of Tuberculosis, The Fourth People's Hospital of Nanning, Nanning, Guangxi, China. Electronic address: zhuqingdong2003@163.com.

BACKGROUND: This study aimed to develop and validate a predictive model based on multimodal data, including clinical features, radiomics features, and deep learning features, to distinguish multidrug-resistant tuberculosis (MDR-TB) in HIV/AIDS patients, thereby improving diagnostic accuracy.
METHODS: A retrospective cohort of HIV/AIDS patients with drug-sensitive tuberculosis (n = 164) and MDR-TB (n = 63) admitted to the Fourth People's Hospital of Nanning between January 2016 and July 2024 was included. The dataset was randomly divided into training and validation sets at a 7:3 ratio. A multimodal model was constructed by integrating a clinical model, a radiomics model, and a 2.5D multi-instance learning (MIL) approach.

RESULTS: Key predictors-platelet count and C-reactive protein-were identified through univariate and multivariate logistic regression analysis. The integrated model achieved the highest performance in both the training and validation set (AUC=0.943 and 0.899, respectively), significantly outperforming individual models. Grad-CAM effectively localized key image regions influencing decision-making, while a nomogram quantified the contribution weights of each predictor, enhancing model transparency. The Hosmer-Lemeshow (HL) test confirmed good model calibration, and the decision curve analysis (DCA) curve demonstrated the optimal clinical net benefit of the integrated model.
CONCLUSION: The multimodal integrated model developed in this study significantly improved the diagnostic efficacy of MDR-TB in HIV/AIDS patients by combining clinical, radiomics, and deep learning features, providing a reliable tool for individualized precision diagnosis and treatment.

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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.

17. Drug-resistance patterns and associated mutations of Mycobacterium tuberculosis strains isolated from chronic kidney disease and diabetes mellitus patients in Ethiopia.

J Glob Antimicrob Resist. 2025 Jun;43:293-300. doi: 10.1016/j.jgar.2025.04.026. Epub 2025 May 12.

Alemu A(1), Diriba G(2), Seid G(3), Mariam SH(2), Berhe N(4), Gumi B(4).

Author information:
(1)Ethiopian Public Health Institute, Addis Ababa, Ethiopia; Aklilu Lemma Institute of Pathobiology, Addis Ababa University, Addis Ababa, Ethiopia. Electronic address: ayinalemal@gmail.com.
(2)Ethiopian Public Health Institute, Addis Ababa, Ethiopia.
(3)Ethiopian Public Health Institute, Addis Ababa, Ethiopia; Aklilu Lemma Institute of Pathobiology, Addis Ababa University, Addis Ababa, Ethiopia.
(4)Aklilu Lemma Institute of Pathobiology, Addis Ababa University, Addis Ababa, Ethiopia.

OBJECTIVE: To assess the drug-resistance (DR) patterns, mutations, and associated factors among tuberculosis (TB) cases identified from diabetes mellitus (DM) and chronic kidney disease patients.
METHODS: The DR patterns of 77 Mycobacterial isolates were assessed using phenotypic drug-susceptibility testing, the Xpert MTB/rifampicin (RIF) assay, the Xpert MTB/XDR assay, and line probe assays. Data were analysed using SPSS version 27. Descriptive statistics, a chi-squared test, and logistic regression were conducted. The 95% CI was determined, and a P-value <0.05 was considered a statistically significant difference.
RESULTS: Resistance pattern was determined for 76 Mycobacterial isolates, and one isolate had an invalid result. Any DR and multi-DR were detected among 25.0% (19), and 7.9% (6) isolates, respectively. Resistance to streptomycin, isoniazid (INH), RIF, ethambutol, and pyrazinamide was 11.8% (9), 13.2% (10), 10.5% (8), 6.6% (5), and 11.8%(9), respectively. Mono-DR was detected for streptomycin 3.9% (3), INH 2.6% (2), RIF 2.6% (2), and pyrazinamide 4.5% (4). One isolate was resistant to fluoroquinolones. Phenotypic and genotypic methods had concordant results in determining RIF and fluoroquinolones resistance. The common RIF and INH-resistant conferring mutations were observed at the S531L and S315T regions, respectively. Previous TB treatment and TB contact history were associated with DR-TB.
CONCLUSIONS: A quarter of TB cases identified had DR-TB, with a higher risk among patients with previous TB treatment history and had contact with TB patients, necessitating programmatic interventions, including applying infection prevention, contact tracing, and access to drug-susceptibility testing using rapid molecular methods.

DOI: 10.1016/j.jgar.2025.04.026
PMID: 40368164 [Indexed for MEDLINE]

18. Healthcare providers' knowledge, attitudes, and perceptions from using targeted sequencing to diagnose and manage drug-resistant tuberculosis (DR-TB) in Eswatini.

PLOS Glob Public Health. 2025 Jun 12;5(6):e0004718. doi: 10.1371/journal.pgph.0004718. eCollection 2025.

Madison M(1)(2)(3), Vambe D(1)(3), Thi SS(4), Ziyane M(5), Shiba N(1)(3), Nkala BB(1)(3), Ness T(3)(6), Lima AV(7), Dlamini S(5), Ngwenya S(4), Mandalakas A(3)(8), Kay A(1)(3).

Author information:

(1)Baylor College of Medicine Children's Foundation Eswatini, Mbabane, Eswatini.
(2)Fulbright U.S. Student Program, New York, New York, United States of America.
(3)The Global Tuberculosis Program, Department of Pediatrics, Baylor College of Medicine, Houston, Texas, United States of America.
(4)National Tuberculosis Control Program, Manzini, Eswatini.
(5)Eswatini, Health Laboratory Services, Mbabane, Eswatini.
(6)Department of Biological Sciences, University of Alaska Anchorage, Anchorage, Alaska, United States of America.
(7)Centro de Investigação em Saúde de Manhiça, Manhiça, Mozambique.
(8)Clinical Infectious Disease Group, German Center for Infectious Research (DZIF) Clinical TB Unit, Research Center Borstel, Borstel, Germany.

Challenges in diagnosing drug-resistant tuberculosis (DR-TB) contribute to a diagnostic gap. Design-locked Targeted Sequencing (TS) assays have the potential to improve DR-TB diagnosis and management. TS assays are now being introduced into low-income, high TB burden settings. Eswatini is among the first high burden countries to have implemented TS for patient care. To evaluate the impact of the current program and optimize future implementation, we evaluated healthcare provider knowledge, attitudes, and perceptions (KAP) of TS and its implementation. We conducted semi-structured interviews with healthcare providers. Interviews were continued until data saturation was reached and analyzed by directed thematic analysis. The study was conducted at 85% of all DR-TB treatment centers (12/14) in rural and urban settings across all four regions in Eswatini. We interviewed nine doctors and eight nurses who were purposively sampled from DR-TB care sites in Eswatini. We found that providers' experience, roles, and settings informed their knowledge and perceptions of DR-TB diagnosis and management. While all healthcare providers wanted to improve comprehensive drug susceptibility testing, operational challenges with the existing program shaped their KAP of TS. In some instances, providers reported that results from TS on sputum improved their ability to provide quality DR-TB patient care. However, they perceived a need for improvements in the delivery of TS results and desired more training to inform their current use of results from sputum and potential future use of results from stool. Overall, healthcare providers recognized TS as an important new tool with the potential to improve DR-TB patient care. However, they also recognized the need for additional healthcare worker training, community engagement, forecasting to avoid reagent shortages, and enhanced medical information systems. Investments in these areas would likely support more effective and sustainable implementation in Eswatini and other LMICs with high TB burdens.

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PMID: 40504844

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

19. Treatment outcomes of drug-resistant tuberculosis in Sabah, Malaysia - a retrospective cohort study.

Public Health Pract (Oxf). 2025 May 9;9:100616. doi: 10.1016/j.puhip.2025.100616. eCollection 2025 Jun.

Lew YL(1), Goroh MMD(1)(2), Yerkovich ST(1)(3), Seow AMH(2), Rajahram GS(4)(5), Teo R(6), Chang AB(1)(3), Lowbridge C(1).

Author information:
(1)Menzies School of Health Research, Charles Darwin University, Northern Territory, Australia.
(2)TB/Leprosy Control Unit, Sabah State Health Department, Kota Kinabalu, Malaysia.
(3)Australian Centre for Health Services Innovation, Queensland University of Technology, Brisbane, QLD, Australia.
(4)Queen Elizabeth II Hospital, Kota Kinabalu, Malaysia.
(5)School of Medicine and Health Science, Monash University Malaysia, Kuala Lumpur, Malaysia.
(6)Public Health Research Section, Sabah State Health Department, Kota Kinabalu, Malaysia.

OBJECTIVES: Addressing drug-resistant tuberculosis (DR-TB) is a priority of the tuberculosis (TB) programme. People with DR-TB frequently have worse outcomes and require more costly and complex management, compared with those with drug-sensitive TB (DS-TB). Our study examined the epidemiology of DR-TB in Sabah, Malaysia, a state with high TB burden. We aimed to identify factors associated with poor treatment outcomes.
STUDY DESIGN: Retrospective cohort study.
METHODS: Data were derived from a national registry of TB patients from Sabah. Descriptive analyses were used to characterise DR-TB epidemiology, including annual trends. Multivariable logistic regression was used to identify factors associated with poor DR-TB treatment outcomes.
RESULTS: Between 2016 and 2021, there were 29,337 registered TB patients, of whom 158 (0.54 %) had DR-TB. The proportion of people with DR-TB between 2016

and 2019 was between 0.32 % and 0.47 % of annual total TB, increasing to 0.97 % in 2021. The proportion of people with DR-TB who were cured or completed treatment (63.1 %) was lower compared with DS-TB (86.0 %). In multivariable analysis, poor DR-TB treatment outcomes (death, lost to follow-up, failed treatment, transferred out & lost) were significantly associated with non-citizen status (adjusted odds ratio [aOR] = 2.49; 95 %CI 1.23-5.13) and male sex (aOR = 2.34; 95 %CI 1.15-4.94).
CONCLUSIONS: There was an increase in the proportion of TB that was DR-TB, coinciding with the COVID-19 pandemic in Sabah. Non-citizens and male sex were the most significant predictors of poor treatment outcomes among those with DR-TB.

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PMID: 40487893

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

20. Healthcare-seeking pathway and delay analysis of rifampicin-resistant tuberculosis patient in Southwestern China.

BMC Public Health. 2025 May 31;25(1):2019. doi: 10.1186/s12889-025-23288-w.

Yang Y(#)(1), Li Z(#)(2), Liu L(1), Chen J(1), Li L(1), Yang R(1), Yang X(1), Chen L(1), Ru H(1), Xu L(3).

Author information:
(1)Division of Tuberculosis Control and Prevention, Yunnan Center for Disease Control and Prevention, Kunming, China.
(2)Kunming Medical University, Kunming, China.
(3)Division of Tuberculosis Control and Prevention, Yunnan Center for Disease Control and Prevention, Kunming, China. xulinth@hotmail.com.
(#)Contributed equally

OBJECTIVES: Rifampicin-resistant tuberculosis (RR-TB) remains a critical health challenge in southwest China. This study investigates healthcare-seeking delays and patient pathways among RR-TB patients in Yunnan province, employing diagram visualization. Aim to explore the accessibility and challenges of medical services for RR-TB.

METHODS: A retrospective cohort study was conducted among RR-TB patients who were enrolled in the Tuberculosis Management Information System (TBMIS) from 2020 to 2022. Data was collected via a face-to-face questionnaire survey to measure the patient pathways and delays of RR-TB patients at different health facility levels. SPSS statistical software was used for descriptive statistics, nonparametric tests, and patient pathway analysis. Sankey diagram, box plot and a heat map were used for data visualization.
RESULTS: Sankey diagrams revealed 7 distinct diagnostic pathways, with 49.4% diagnosed after one health facility visit. Over 50% of patients were diagnosed at county level facilities (Level 2), prolonging delays. As the level of health facility increases, the flow of RR-TB patients gradually decreased. Treatment pathways were simple with 4 routes. 92.4% of RR-TB patients enrolled treatment after visiting only one health facility, reflecting shorter treatment delays (median: 5 days). The median total delay was 66 days (Interquartile range: 28 to 155) of RR-TB patients. The diagnostic delay and total delay in lower health facilities was significantly higher than that in higher-levels ($P < 0.05$).
CONCLUSIONS: This study visualizes RR-TB healthcare-seeking flows in economically underdeveloped areas of China. Though healthcare access is decent, diagnostic delays are notable, especially at under-resourced facilities. We should pay more attention to and enhance the RR-TB diagnostic capabilities of primary health facilities. While treatment pathways are simple, financial burdens might be a key issue. Reducing these burdens through multi-channel funding and policy support is essential.

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PMCID: PMC12125907
PMID: 40450248 [Indexed for MEDLINE]

Conflict of interest statement: Declarations. Ethics approval and consent to participate: This study was consulted to “the ethics committees of Yunnan Center for Disease Control and Prevention” (Ethical review approval document 2023-34). We informed consent to participate was obtained from all of the participants in the study. The study did not include any data of patients’ personal information, including name, identity information, address, telephone number, etc. Our study complies with the Declaration of Helsinki. Consent for publication: Not applicable. Competing interests: The authors declare no competing interests.

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

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

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

Global health is threatened by the rise of antibiotic resistance. Bacteria of the Mycobacterium tuberculosis complex (Mtbc) are a major contributor to this antibiotic crisis, with about 450,000 new multidrug-resistant tuberculosis (MDR-TB) cases per year. This study investigates resistance evolution by defining the resistance mutant selection window (MSW) for the important MDR-TB treatment drugs moxifloxacin and bedaquiline. We employed a combination of long-term in vitro experiments supplemented with mathematical modeling that combined pharmacodynamics with population genetics. We assessed resistance selection at concentrations below the minimum inhibitory concentration (MIC), the MSW and fitness cost of eight mutant clones with different resistance-associated variants. Both computational and experimental results show that mutant clone populations are selected far below the MIC, leading to a major growth advantage of resistant populations under weak selection pressure. An eighth of the MIC was enough to enrich mutant clone populations in the short term (five bacterial passages or 20 generations), even in mutant clones with a major competitive fitness loss. In fact, gyrA, gyrB and most Rv0678 mutations have virtually no effect on the bacteria's competitive fitness in vitro. This work highlights the risk that ineffective drug delivery and dosing can lead to the emergence of resistance.

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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.

22. Deciphering linezolid-induced hematologic toxicity: Targeting TOP2A and TOP2B via its primary metabolite PNU142586.

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Thu VTA(1)(2), Nhu NQ(1), Anh NTV(1)(2), Lim SA(1), Seong HJ(1)(2), Md Rasheduzzaman J(1)(2), Kim U(3), Cho HS(3)(4), Soedarsono S(5)(6), Shin JG(1)(2)(7), Cho YS(1)(2)(7).

Author information:
(1)Center for Personalized Precision Medicine of Tuberculosis, Inje University College of Medicine, Busan, Korea.
(2)Department of Pharmacology and PharmacoGenomics Research Center, Inje University College of Medicine, Busan, Korea.
(3)Department of Systems Biology, Yonsei University, Seoul 03722, Republic of Korea.
(4)Institute for Bio-medical Convergence Science and Technology, Yonsei University, Seoul 03722, Republic of Korea.
(5)Sub-pulmonology Department of Internal Medicine, Faculty of Medicine, Hang Tuah University, Surabaya, Indonesia.
(6)Dr. Soetomo Academic General Hospital, Surabaya, Indonesia.
(7)Department of Clinical Pharmacology, Inje University Busan Paik Hospital, Busan, Korea.

Linezolid, an oxazolidinone antibiotic, is widely used to treat multidrug-resistant tuberculosis and drug-resistant Gram-positive infections. However, prolonged use is associated with severe hematologic toxicity, the underlying mechanisms of which remain incompletely understood, particularly regarding the role of linezolid metabolites. Our clinical study indicates that elevated exposure to PNU142586, a primary metabolite of linezolid, is associated with an increased risk of linezolid-induced toxicity, even in the absence of

renal impairment. To elucidate its mechanism, we identify DNA topoisomerase 2-α (TOP2A) and DNA topoisomerase 2-β (TOP2B) as primary targets of PNU142586 at molecular, cellular, and in vivo levels. PNU142586 disrupts replication and transcription by impeding DNA binding to TOP2A and TOP2B with a favorable conformation for cleavage and by inhibiting adenosine 5'-triphosphate hydrolysis, ultimately leading to antiproliferative and cytotoxic effects, including mitochondrial dysfunction. The present study thus provides mechanistic insight into linezolid-induced hematologic toxicity and offers a foundation for safer antibiotic development and improved clinical monitoring through biomarker identification.

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PMID: 40435237 [Indexed for MEDLINE]

23.Human Gut Bacteriophageome: Insights Into Drug Resistance Mechanisms in Tuberculosis.

Interdiscip Perspect Infect Dis. 2025 Jun 16;2025:8811027. doi: 10.1155/ipid/8811027. eCollection 2025.

Jafari E(1)(2), Azizian R(1)(2), Tabasi M(3), Banakar M(4)(5), Bagheri Lankarani K(4).

Author information:
(1)Pediatric Infectious Diseases Research Center (PIDRC), Tehran University of Medical Sciences, Tehran 14197, Iran.
(2)Biomedical Innovation and Start-Up Student Association (Biomino), Tehran University of Medical Sciences, Tehran 14317, Iran.
(3)Center for Inflammation and Lung Research, Temple University, Philadelphia 19140, Pennsylvania, USA.
(4)Health Policy Research Center, Shiraz University of Medical Sciences, Shiraz 71348, Fars, Iran.
(5)Dental Research Center, Tehran University of Medical Sciences, Tehran 14399, Iran.

Tuberculosis (TB), caused by Mycobacterium tuberculosis, remains a major global health burden. The emergence of drug-resistant strains presents a critical challenge in TB management. The recent research has explored the interaction between TB and the human gut bacteriophage community (phageome). The gut phageome plays a crucial role in regulating microbial diversity and functionality, and its composition and function have been linked to various health conditions. Examining the gut phageome through metagenomic analysis

provides insights into its composition, role in health, and interactions with the host immune system. Exploring the interaction between the gut phageome and M. tuberculosis may reveal how phages affect the bacterium's pathogenicity, survival, and mechanisms of drug resistance. Understanding the gut phageome's impact on TB drug resistance could inform novel therapeutic strategies, such as phage therapy, and highlight the importance of microbiome-based interventions in combating drug-resistant TB strains. This review explores the role of the gut phageome in influencing drug resistance in TB, focusing on interaction mechanisms and potential therapeutic implications, synthesizing current research findings, and identifying knowledge gaps in this emerging field. This review also synthesizes the current evidence on the gut phageome's role in TB drug resistance, focusing on phage-mediated horizontal gene transfer (e.g., rpoB, katG), immune modulation, and preclinical efficacy of mycobacteriophage therapies. Key findings highlight phage cocktails (e.g., DS6A, D29 LysB) as promising adjuncts to antibiotics, reducing M. tuberculosis burden in murine models. These insights advocate for phage therapy as a complementary strategy against drug-resistant TB, urging clinical validation to bridge the existing knowledge gaps.

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PMID: 40552317

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24. The Usefulness of the BD MAX MDR-TB Molecular Test in the Rapid Diagnosis of Multidrug-Resistant Tuberculosis.

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Bogiel T(1)(2), Dolska E(3), Zimna M(3), Nakonowska K(3), Krawiecka D(3), Żebracka R(3), Pochowski M(3), Krawczyk A(4).

Author information:
(1)Department of Propaedeutics of Medicine and Infection Prevention Ludwik Rydygier Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Toruń, 9 Maria Skłodowska-Curie Street, 85-094 Bydgoszcz, Poland.
(2)Clinical Microbiology Laboratory, Dr. Antoni Jurasz University Hospital No. 1 in Bydgoszcz, 9 Maria Skłodowska-Curie Street, 85-094 Bydgoszcz, Poland.
(3)Department of Microbiological Diagnostics, Kujawsko-Pomorskie Pulmonology

Centre in Bydgoszcz, 85-326 Bydgoszcz, Poland.
(4)Department of Molecular Medical Microbiology, Chair of Microbiology, Jagiellonian University Medical College, 31-121 Kraków, Poland.

Tuberculosis (TB), primarily caused by Mycobacterium tuberculosis complex (MTBC), remains a global health challenge and can lead to severe pulmonary and extrapulmonary complications. Multidrug-resistant TB (MDR-TB) poses additional challenges, requiring advanced diagnostic and treatment strategies. This study evaluates the BD MAX MDR-TB molecular test for a rapid diagnosis of MDR-TB, detecting resistance to rifampicin (RIF) and isoniazid (INH). The BD MAX MDR-TB test, utilizing real-time PCR, was used to analyze specimens collected from TB-suspected patients, identifying MTB DNA and mutations associated with rifampicin and isoniazid resistance. Results were compared with traditional drug susceptibility testing, and 79 out of 638 samples tested were positive for MTB DNA, with 65 showing a sufficient amount of genetic material for resistance gene identification. The BD MAX test showed a 100% correlation with phenotypic rifampicin resistance, though discrepancies were noted for isoniazid resistance, with a 93% concordance. The BD MAX MDR-TB test is an effective tool for a rapid diagnosis of MDR-TB, especially for rifampicin resistance. However, it may not detect certain mutations related to isoniazid resistance. Complementary tests like Xpert MTB/XDR or whole-genome sequencing could improve diagnostic accuracy and support more effective TB control strategies.

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25. Prevalence of drug-resistant Mycobacterium tuberculosis and its associated factors among tuberculosis patients attending Dilla university referral hospital, Ethiopia.

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Hatiya M(1)(2), Merid Y(3), Mola A(4), Belayneh F(5), Ali MM(3).

Author information:
(1)Hawassa Health Science College, Hawassa, Ethiopia. melat5442@gmail.com.
(2)College of Medicine and Health Sciences, School of Medical Laboratory Science, Hawassa University, Hawassa, Ethiopia. melat5442@gmail.com.
(3)College of Medicine and Health Sciences, School of Medical Laboratory Science, Hawassa University, Hawassa, Ethiopia.

(4)Centeral Ethiopia Region Public Health Institute Laboratory, Worabe, Ethiopia.
(5)College of Medicine and Health Sciences, School of Public Health, Hawassa University, Hawassa, Ethiopia.

BACKGROUND: Tuberculosis (TB) is an infectious disease caused by Mycobacterium tuberculosis (MTB) and is the second leading cause of death from contagious diseases worldwide. Ethiopia is among the 30 countries with the highest burden of TB and TB/HIV co-infection. The emergence and spread of drug-resistant TB present significant challenges to TB care and control efforts, particularly multi-drug-resistant TB, which poses a serious public health issue in low-income countries such as Ethiopia. This study aimed to determine the prevalence of drug-resistant TB and its associated factors among TB patients in Dilla University Referral Hospital (DURH).
METHOD: A prospective cross-sectional study was conducted from March-2024 to May-2024 among 216 pulmonary TB patients attending DURH. Gene Xpert MTB/RIF Ultra and Xpert MTB/XDR assay was used to assess the pattern of drug resistance in TB. The Xpert MTB/RIF Ultra assay was used to detect rifampicin resistance, while the Xpert MTB/XDR assay was employed to identify isoniazid resistance and resistance to second-line anti-TB drugs when rifampicin resistance was detected. Data were analyzed by using the Statistical Package for Social Sciences (SPSS) version 25.
RESULT: In this study, out of 216 confirmed MTB cases, 5 (2.3%) were identified as drug-resistant TB (DR-TB), with mono-resistance to rifampicin and isoniazid at 1.4% and 0.9%, respectively. The statistical analysis revealed a significant difference in DR-TB prevalence between those with and without a history of anti-TB treatment ($p = 0.001$). Notably, isoniazid mono-resistant TB was more prevalent among individuals with diabetes mellitus and those with a history of previous treatment, showing p-values of 0.018 and 0.015, respectively.
CONCLUSION: Among the 216 confirmed TB cases, 5 cases of DR-TB were identified, accounting for 2.3%. DR-TB was more prevalent in patients with a history of anti-TB treatment, highlighting the urgent need for enhanced early detection and improved treatment monitoring. Additionally, isoniazid mono-resistant TB was notably prevalent in individuals with diabetes mellitus and prior treatment history, with p-values of 0.018 and 0.015, respectively. Targeted interventions for these high-risk groups are essential to address drug resistance in TB, enabling us to effectively tackle the emergence of drug-resistant TB at both local and national levels.

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PMID: 40481411 [Indexed for MEDLINE]

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

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

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

Fluoroquinolones (FQs) resistance in Mycobacterium tuberculosis (MTB), primarily driven by mutations in the quinolone resistance-determining region (QRDR) of gyrA, poses a major concern in treating for multidrug-resistant tuberculosis (MDR-TB). These QRDR mutations are known to confer varying levels of resistance, leading to differences in treatment outcomes. Here, we introduced the MeltArray MTB/FQs assay, a multiplex PCR method that detected 11 gyrA-QRDR mutations and quantified their fractions via a polynomial regression algorithm-based formula, enabling mutation identification and quantification within 3 h in one reaction. This assay, with a limit of detection (LOD) of 50 copies/reaction, could identify mixtures containing 5% mutant gDNA across 50 to 50,000 copies/reaction. Clinical evaluation of 442 culture samples displayed 95.23% sensitivity and 99.32% specificity compared with phenotypic antimicrobial susceptibility testing (pAST). Evaluation of 121 paired sputum-culture samples revealed sensitivities of 90.32% in sputum samples and 95.24% in culture samples, both with specificities of 100%, when compared with pAST. Further evaluation of 285 sputum

samples showed 93.75% positive percent agreement (PPA) and 98.10% negative percent agreement (NPA) in comparison with the MeltPro MTB/FQs kit (Zeesan Biotech, China). All mutant samples identified by MeltArray MTB/FQs but classified as susceptible by pAST or as wild type by MeltPro MTB/FQs were confirmed through Sanger sequencing and droplet digital PCR (ddPCR). The formula for predicting mutation fraction (MUT%) showed accuracy rates of 88.00%, 88.89%, and 83.33% in the training, validation, and test data sets, respectively, when compared with ddPCR results. Overall, MeltArray MTB/FQs assay offers an upgraded alternative for routine FQs resistance monitoring.IMPORTANCERising FQs resistance has driven the spread of pre-extensively drug-resistant tuberculosis (pre-XDR-TB), challenging global tuberculosis (TB) control efforts. Conventional molecular assays for FQs resistance often cannot distinguish between low-level and high-level resistance mutations or detect low-fraction heteroresistant populations. In this study, we established a MeltArray MTB/FQs assay that can identify all the 11 critical mutations in the gyrA-QRDR with a LOD of 50 copies/reaction, enabling direct, culture-independent analysis of sputum samples. By using an algorithm to quantify mutations at levels as low as 5% in mixtures, MeltArray achieved both mutation identification and quantification within 3 h in a reaction, thus providing a powerful tool for early detection and precise management of pre-XDR-TB.

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27. Patient and health system delays in the diagnosis and treatment of tuberculosis in Gandaki, Nepal.

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Dhami BS(1), Paneru DP(1), Parajuli S(1), Aarati KC(1), Nath D(1)(2).

Author information:
(1)School of Health and Allied Sciences, Pokhara University, Pokhara, Gandaki Province, Nepal.
(2)Health Directorate, Ministry of Social Development, Doti, Sudurpashchim Province, Nepal.

Delays in accessing healthcare worsen disease outcomes, increasing Tuberculosis (TB) transmission rates and mortality. Prolonged delays may contribute to drug-resistant TB strains in some cases, this study assessed delays in diagnosis and treatment among TB patients in Gandaki, Nepal. A cross-sectional study was conducted among a randomly selected sample of 194 TB patients enrolled in Direct

Observed Treatment Short-course (DOTS) therapy. The data were collected through face-to-face interviews using a semi-structured interview schedule, which was developed through literature review and adaptation of the World Health Organization's multi-country study. Multivariate logistic regression was employed to identify factors associated with delays in diagnosis and treatment, considering a p value < 0.05 to indicate statistical significance. The median patient and health system delays were 35 (7-120) and 9 (2-98) days, respectively. Furthermore, 55.7% and 58.2% of patients experienced patient and health system delays, respectively. In the multivariable logistic regression analysis, factors associated with unacceptable patient delay included non enrollment in government health insurance programmes (AOR: 3.19; 95% CI: 1.29-7.98), seeking care from non-National Tuberculosis Program (non-NTP) providers (AOR: 3.19; 95% CI: 1.460-6.97), poor knowledge of TB (AOR: 3.74; 95% CI: 1.67-8.37), and high levels of perceived stigma (AOR: 3.15; 95% CI: 1.42-6.94). Furthermore, undergoing an initial diagnostic test other than GeneXpert (AOR: 3.25; 95% CI: 1.19-8.87) and visiting healthcare facilities multiple times before being diagnosed with TB (AOR: 5.62; 95% CI: 2.26-13.96) were significantly associated with unacceptable health system delay. Patient and health system delays were prevalent among TB patients. Reducing these delays is crucial for improving TB control. Therefore, urgent action is needed to implement education campaigns to improve TB literacy. Additionally, engaging private and informal healthcare providers and enhancing their capacity to deliver timely and effective TB care could potentially mitigate delays in diagnosis and treatment.

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PMID: 40471951

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

28. Characterizing Musculoskeletal and Neurological Toxicities Associated With the BPaLM Regimen: A Clinical Evaluation of Arthralgia and Peripheral Neuropathy in Patients With Multidrug-Resistant Tuberculosis (MDR-TB).

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Khan Z(1), Ali G(2), Rumman(3)(4), Ashraf(5), Naveed A(6), Salam S(7), Ullah U(8)(9), Ismail A(10), Altaf A(11).

Author information:
(1)Orthopedic Surgery, Medical Teaching Institution (MTI) Mardan Medical Complex, Bacha Khan Medical College, Mardan, PAK.
(2)Neurosurgery, Medical Teaching Institution (MTI) Mardan Medical Complex, Bacha Khan Medical College, Mardan, PAK.
(3)Pharmacovigilance/Active Drug Safety Monitoring and Management, Medical Teaching Institution (MTI) Mardan Medical Complex, Mardan, PAK.
(4)Pharmacovigilance/Active Drug Safety Monitoring and Management, Association for Community Development, Peshawar, PAK.
(5)Research and Development, Pro-Gene Diagnostics and Research Laboratory, Mardan, PAK.
(6)Epidemiology and Public Health, Association for Community Development, Peshawar, PAK.
(7)Pulmonology, Provincial Tuberculosis Control Program, Directorate of Health, Peshawar, PAK.
(8)Tuberculosis, Association For Community Development, Peshawar, PAK.
(9)Pulmonology, Medical Teaching Institution (MTI) Mardan Medical Complex, Mardan, PAK.
(10)Epidemiology and Public Health, National Tuberculosis Control Program, Ministry of National Health Services, Regulations, and Coordination, Islamabad, PAK.
(11)Cardiology, Rehman Medical Institute, Peshawar, PAK.

BACKGROUND: Musculoskeletal and neurological toxicities are common side effects of the BPaLM (bedaquiline, pretomanid, linezolid, and moxifloxacin) regimen, an emerging treatment for multidrug-resistant tuberculosis (MDR-TB). These toxicities, particularly arthralgia and peripheral neuropathy, can significantly impair the quality of life of patients undergoing treatment. Despite the promising therapeutic benefits of the BPaLM regimen, the prevalence and severity of these side effects remain underexplored. Understanding these toxicities is crucial to improving patient management strategies and ensuring better treatment adherence.
OBJECTIVE: This study aims to determine how common and severe musculoskeletal and neurological toxicities, particularly arthralgia and peripheral neuropathy, are among MDR-TB patients treated with the BPaLM regimen.
MATERIALS AND METHODS: This prospective observational study was conducted at the Programmatic Management of Drug-Resistant Tuberculosis in Mardan Medical Complex between January 2024 and April 2025. Patients with MDR-TB undergoing treatment with the BPaLM regimen were monitored for musculoskeletal and neurological toxicities, specifically arthralgia and peripheral neuropathy. Clinical

evaluations included assessing the onset, severity, and impact of joint pain and nerve damage, as well as evaluating the effectiveness of pain management and physical therapy interventions. Data collection included demographic information, comorbidities, and baseline physical activity levels. Statistical analysis was performed using SPSS Statistics version 26 (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp.), Python (Python Software Foundation, Beaverton, OR, USA), and R 4.4.5 (R Foundation for Statistical Computing, Vienna, Austria) to identify significant predictors of toxicity severity through descriptive statistics, chi-square tests, and decision tree modeling. Kaplan-Meier survival analysis was also conducted to assess the relationship between toxicity severity and treatment outcomes.
RESULTS: Among the 44 MDR-TB patients, 35 (79.54%) experienced mild to moderate arthralgia, with knee pain being most common (34, 77.27%). Peripheral neuropathy was reported in 26 (59.09%) patients, with the lower limbs (20, 45.45%) being most affected. Kaplan-Meier survival analysis revealed a significant difference in survival times based on the severity of arthralgia and peripheral neuropathy, with more severe symptoms correlating with reduced survival duration.
CONCLUSIONS: The findings underscore the importance of early identification, regular monitoring, and personalized management strategies to mitigate the burden of these toxicities and enhance patient outcomes.

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and diagnostic aspects of drug-resistant tuberculosis. This project was supported by the Global Fund, World Health Organization (WHO), USAID, TB Alliance, and the Bill & Melinda Gates Foundation, with funding from Australia's Department of Foreign Affairs and Trade, Germany's Federal Ministry of Education and Research through KfW, Irish Aid, and the Foreign, Commonwealth and Development Office (United Kingdom), focusing on treatment and diagnostic aspects of drug-resistant tuberculosis. from World Health Organization (WHO) declare(s) treatment and diagnostic aspects of drug-resistant tuberculosis. This project was supported by the Global Fund, World Health Organization (WHO), USAID, TB Alliance, and the Bill & Melinda Gates Foundation, with funding from Australia's Department of Foreign Affairs and Trade, Germany's Federal Ministry of Education and Research through KfW, Irish Aid, and the Foreign, Commonwealth and Development Office (United Kingdom), focusing on treatment and diagnostic aspects of drug-resistant tuberculosis. World Health Organization (WHO) declare(s) treatment and diagnostic aspects of drug-resistant tuberculosis. This project was supported by the Global Fund, World Health Organization (WHO), USAID, TB Alliance, and the Bill & Melinda Gates Foundation, with funding from Australia's Department of Foreign Affairs and Trade, Germany's Federal Ministry of Education and Research through KfW, Irish Aid, and the Foreign, Commonwealth and Development Office (United Kingdom), focusing on treatment and diagnostic aspects of drug-resistant tuberculosis. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

29. Nurse-led palliative care for multidrug-resistant tuberculosis: a parallel, single-blind, pragmatic, randomised controlled trial in Uganda.

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Buyinza N(1), Nkhoma K(2), Namisango E(3), Maddocks M(2), Downing J(4), Prevost AT(2), Chukwusa E(2), Harding R(5).

Author information:
(1)Hospice Africa Uganda, Makindye, Kampala, Uganda.
(2)Florence Nightingale Faculty of Nursing Midwifery & Palliative Care, King's College London, London, UK.
(3)African Palliative Care Association, Kampala, Uganda.
(4)International Children's Palliative Care Network, Bristol, UK.
(5)Florence Nightingale Faculty of Nursing Midwifery & Palliative Care, King's College London, London, UK. Electronic address: richard.harding@kcl.ac.uk.

BACKGROUND: People with multidrug-resistant tuberculosis experience burdensome

symptoms, clinical uncertainty, and high mortality. Palliative care is a designated essential health service under Universal Health Coverage. We aimed to test the hypothesis that receipt of additional nurse-led palliative care would improve patient-reported outcomes for patients with multidrug-resistant tuberculosis, compared with usual care.
METHODS: This single-masked, parallel pragmatic randomised controlled trial recruited adults from three public hospitals in Uganda (Mulago National Referral Hospital Kampala, Gulu Regional Referral Hospital, and Mbale Regional Referral Hospital). Inclusion criteria for the study were adults aged 18 years and older with a confirmed bacteriological diagnosis of multidrug-resistant tuberculosis (not responsive to isoniazid or rifampicin) who were registered at the respective study site clinics and who were able to give informed consent. Participants were randomly assigned (1:1) to the intervention (additional nurse-led care) or the standard care control group using randomly permuted blocks stratified by treatment centre. Intervention group participants received nurse-led person-centred holistic assessment, care planning, symptom control, and psychosocial support delivered on inpatient wards or at home. Fortnightly appointments alternated between face-to-face visits and telephone follow-up. Researchers were masked to participant group allocation. The primary outcome was multidimensional palliative care-related symptoms and concerns measured using the African Palliative Care Association Integrated Palliative Outcome Scale, measured monthly from baseline to the primary 4-month endpoint, analysed using a linear mixed-effect model, applying the intention-to-treat principle to analyse participants by allocated group. The trial was registered on the ISRCTN registry (ISRCTN13664346) and is complete.
FINDINGS: Between Dec 18, 2019, and Sept 10, 2020, 178 individuals were initially assessed for eligibility, 24 were excluded for not meeting inclusion criteria, declining to participate, or being too ill to participate, and 154 participants were recruited and randomly assigned to the intervention group or the control group. 76 were assigned to the nurse-led palliative care group and 78 were assigned to the control group. 52 (34%) participants were female and 102 (66%) were male and participants had an overall median age of 38 years (IQR 31-46). From the linear mixed-effects model the intervention had a significant positive effect compared with standard care (5·12 scale-points [95% CI 2·89-7·21], p<0·0001) at the 4-month follow-up. The standardised effect size was 0·61 (95% CI 0·35-0·86).
INTERPRETATION: Additional nurse-led palliative care for patients with multidrug-resistant tuberculosis improved self-reported outcomes spanning physical, psychological, social, and spiritual domains, and increased medication adherence. Person-centred assessment and holistic care with pain and symptom control should be task-shifted into routine tuberculosis care.
FUNDING: Open Society Foundations.

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PMID: 40412430

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

30.Hearing Impairment Among Drug-Resistant Tuberculosis Patients in Rural Eastern Cape: A Retrospective Analysis of Audiometric Findings.

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Faye LM(1), Hosu MC(1), Dlatu N(2), Henge-Daweti V(1), Apalata T(1).

Author information:
(1)Department of Laboratory Medicine and Pathology, Faculty of Medicine and Health Sciences, Walter Sisulu University, Mthatha 5117, South Africa.
(2)Department of Public Health, Faculty of Health Sciences, Walter Sisulu University, Private Bag X1, Mthatha 5117, South Africa.

Hearing loss (HL) is a major global health concern, with drug-induced ototoxicity contributing significantly, particularly in patients undergoing treatment for drug-resistant tuberculosis (DR-TB). In South Africa, where both TB and HIV are prevalent, the risk of treatment-related auditory damage is especially high. This study aimed to assess the prevalence and predictors of hearing impairment among DR-TB patients in rural Eastern Cape, South Africa. A retrospective analysis was conducted on 438 DR-TB patients treated between 2018 and 2020, using pure tone audiometry (PTA) to assess hearing status post-treatment. Demographic, clinical, and lifestyle data were extracted from patient records and analyzed using logistic regression. The overall prevalence of hearing loss was 37.2%. Risk was significantly associated with an older age, a male gender, DR-TB classification (MDR, pre-XDR, and XDR), unsuccessful treatment outcomes, and substance use. Prevalence of HL increased notably in patients aged 70 and older. Lifestyle factors, particularly combined use of tobacco, alcohol, and drugs, were linked to higher odds of HL. These findings underscore the need for routine audiometric screening and personalized treatment monitoring in DR-TB care, especially for high-risk populations. Early identification of ototoxicity risk factors can inform safer treatment regimens and improve patient outcomes in resource-limited settings.

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31. Non-communicable diseases and resistant tuberculosis, a growing burden among people living with HIV in Eastern Kenya.

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Muriuki PK(1), Ngayo MO(2), Njire M(3), Mungiria J(2), Nyanya WA(2), Owuor D(2), Ndung'u P(1).

Author information:
(1)Department of Medical Laboratory Science, Jomo Kenyatta University of Agriculture and Technology, Kenya.
(2)Centre of Microbiology Research, Kenya Medical Research Institute, Nairobi, Kenya.
(3)Department of Biochemistry and Molecular Biology, Jomo Kenyatta University of Agriculture and Technology, Kenya.

Human Immunodeficiency Virus (HIV) and tuberculosis (TB) continue to pose a significant health burden in Kenya. Countries with the highest rates of people living with HIV (PLWH) also have a high prevalence of non-communicable diseases (NCDs), including type 2 diabetes (T2D) and hypertension (HPT). This study evaluated the burden and factors associated with T2D, HPT, and TB, including resistant strains among PLWH receiving antiretroviral therapy (ART) in Eastern Kenya. Blood and sputum samples, and baseline information were collected from 280 consenting PLWH. The participants' blood pressure (BP), glycated hemoglobin (HbA1c), CD4 cell counts, HIV viral load, full blood count, blood chemistry, and Rifampicin resistance were assessed. The mean (SD) age of the participants was 35.6 (±9.8) years, and a median (IQR) duration of living with HIV of 7 (4 -8) years. Most participants, 179 (63.9%), were HIV mono-infected, with 58 (20.7%) HIV/TB, 42 (15%) HIV/T2D, and 33 (11.8%) HIV/HPT dual comorbidities reported. Triple comorbidities reported included 18 (6.4%) HIV/T2D/HPT, 9 (3.2%) HIV/TB/T2D, and 9 (3.2%) HIV/TB/HPT, with 4 (1.4%) HIV/TB/T2D/HPT quadruple comorbidity reported. Six (2.1%) multidrug-resistant TB coinfections were detected. In multivariate analyses, being on ARV only (aOR 0.5; 95% CI 0.4 -

0.6, p = 0.0001) and achieving virological suppression (aOR 0.8; 95% CI 0.6 - 0.9, p = 0.017) were protective against HIV/TB coinfection. Previous hospital admission (aOR 1.2; 95% CI 1.1 - 1.4, p = 0.049) and previous TB infection (aOR 1.6; 95% CI 1.0 - 3.0, p = 0.034) were associated with HIV/TB coinfection. The PLWH in Eastern Kenya continues to experience a syndemic of NCDs and TB, including resistant strains. Consistent adherence to ART is crucial for achieving viral suppression; these are protective against NCDs and TB among PLWH. The findings highlight the necessity of integrating NCD management with HIV and TB treatment programs in Kenya.

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32.Risk factors associated with morbidity and unfavorable treatment outcome in drug-resistant pulmonary tuberculosis: a case-control study.

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Li C(1), Liang S(1), Wang X(1), Lui S(2), Wang C(1).

Author information:
(1)Department of Pulmonary and Critical Care Medicine, Targeted Tracer Research and Development Laboratory, Frontiers Science Center for Disease-Related Molecular Network, State Key Laboratory of Respiratory Health and Multimorbidity, West China Hospital, West China School of Medicine, Sichuan University, Chengdu 610041, China.
(2)Department of Radiology, and Functional and Molecular Imaging Key Laboratory of Sichuan Province, Huaxi MR Research Center (HMRRC), Research Unit of Psychoradiology, Chinese Academy of Medical Sciences, West China Hospital, West China School of Medicine, Sichuan University, Chengdu 610041, China.

OBJECTIVES: To investigate the risk factors in patients with drug-resistant tuberculosis (DR-TB) and clinical characteristics related to unfavorable anti-TB

treatment outcomes.
METHODS: A total of 961 pulmonary tuberculosis (TB) patients were included at West China Hospital of Sichuan University from January 2008 to November 2023. We analyzed the differences of clinical characteristics between DR-TB and drug-sensitive tuberculosis (DS-TB), and then compared these features in DR-TB patients with different outcomes. Multivariable logistic regression models were employed to quantify risk factors associated with DR-TB and adverse treatment outcomes.
RESULTS: Among 961 pulmonary TB patients, a history of anti-TB treatment [odds ratio (OR), 3.289; 95% confidence interval (CI), 2.359-4.604] and CT-scan cavities (OR, 1.512; 95% CI, 1.052-2.168) increased DR-TB risk. A total of 214 DR-TB patients were followed for a median of 24.5 months. Among them, 116/214 (54.2%) patients achieved favorable outcomes. Prior anti-TB treatment (OR, 1.927; 95% CI, 1.033-3.640), multidrug-resistant tuberculosis (MDR-TB) (OR, 2.558; 95% CI, 1.272-5.252), positive sputum bacteriology (OR, 2.116; 95% CI, 1.100-4.134), and pleural effusion (OR, 2.097; 95% CI, 1.093-4.082) were associated with unfavorable outcomes, while isoniazid-resistant TB patients showed better outcomes (OR, 0.401; 95% CI, 0.181-0.853). The clinical model for unfavorable outcome prediction of DR-TB achieved an area under the curve (AUC) of 0.754 (95% CI, 0.690-0.818).
CONCLUSIONS: Treatment history of anti-TB not only increases the risk of the emergence of DR-TB, but also potentially leads to treatment failure during re-treatment in DR-TB patients. Drug resistance subtypes, radiological characteristics, and the results of sputum smear or culture may affect the treatment outcome of DR-TB.

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Conflict of interest statement: None declared.

33. Drug resistance profile of Mycobacterium tuberculosis complex isolated from pulmonary tuberculosis patients and their household contacts in central Ethiopia.

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Drug resistance profile of Mycobacterium tuberculosis complex isolated from pulmonary tuberculosis patients and their household contacts in central

Ethiopia.

Seid G(1)(2), Alemu A(3)(4), Diriba G(3), Zerihun B(3), Tadesse G(3), Mariam SH(4), Gumi B(4).

Author information:
(1)Ethiopian Public Health Institute, P.O. Box 1242, Addis Ababa, Ethiopia. gech1365@gmail.com.
(2)Aklilu Lemma Institute of Pathobiology, Addis Ababa University, P.O. Box 1176, Addis Ababa, Ethiopia. gech1365@gmail.com.
(3)Ethiopian Public Health Institute, P.O. Box 1242, Addis Ababa, Ethiopia.
(4)Aklilu Lemma Institute of Pathobiology, Addis Ababa University, P.O. Box 1176, Addis Ababa, Ethiopia.

BACKGROUND: There is a gap between tuberculosis (TB) infection and the onset of clinical TB disease, which makes identifying TB transmission dynamics a prominent challenge. Different reports were made on the concordance of drug-resistance profiles between the household contact and the purported index case. This study investigated the drug-resistance pattern concordance of the index-household contact pair in central Ethiopia.
METHOD: A laboratory-based cross-sectional study was conducted on Mycobacterium tuberculosis isolates identified from bacteriologically confirmed pulmonary TB patients and their household contacts (HHCs) in central Ethiopia from January to December 2023. Sputum specimens were collected from index cases and presumptive HHCs and examined using the Xpert Ultra assay, Xpert XDR assay, and Mycobacterium tuberculosis culture. Descriptive statistics were used to summarize the data.
RESULT: Among 902 TB symptoms screened HHCs of 303 index cases, 20.17% (182/902) had Presumptive TB, and 7.14% (13/182) developed active tuberculosis. In index cases, 23.52% (64 /272) showed resistance to at least one of the five first-line anti-TB drugs. The prevalence of mono-resistant to STR, INH, RIF, and PZA was: 2.20% (6 /272), 2.20% (6/272), 6.25% (17/272), and 1.47% (4/272), respectively. Any first-line anti-TB drug resistance was higher among relapse cases than new cases, at 41.67% (10/24) and 21.77% (54/248), respectively. Among the RR/MDR-TB cases tested with the Xpert MTB/XDR assay, 56.81% (25/44) cases showed resistance to INH. Among these 25 INH resistance samples, 5 had no melting point on the wild ahpc gene as well as on the ahpc gene mutant. In HHCs with positive cultures, 23.07% (3/13) displayed resistance to any first-line anti-TB medication. Only 69.23% (9/13) of HHCs had isolates that aligned with the pDST pattern of the index case for all five first-line anti-TB drugs.
CONCLUSION: Nearly one-third of the household contacts have discordant drug-resistance profiles from the index patients. This study offers compelling proof that it is not advisable to treat close contacts without DST results based on the DST results of the supposed source case. The low drug resistance rate to

new oral second-line drugs in this study did not guarantee the absence of resistance to each drug.

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

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

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

Multidrug-resistant (MDR) strains of Mycobacterium tuberculosis represent an obstacle to eradicating tuberculosis (TB) due to the low treatment success rate of MDR TB. Among them, the MDR B0/W148 clone has recently evolved from the M. tuberculosis Beijing lineage 2 and is widely disseminated in Russia and Europe. To get more insights into the genetic factors underlying the evolutionary success of the MDR M. tuberculosis B0/W148 clone in addition to environmental and patient-related features, we focused on two mutations specific to this clone that are found in the transcriptional regulators WhiB6 and KdpDE and

investigated in a H37Rv strain background the transcriptional profile associated with these mutations and their impact on the in vitro and in vivo growth characteristics. Through the construction and use of H37RvΔwhiB6, H37RvΔkdpDE, and complemented strains, neither mutation impaired the in vitro growth of M. tuberculosis in standard mycobacterial growth media. The mutation T51P in whiB6 prevented the upregulation of 9 genes in the esx-1 core region and 44 genes elsewhere in the genome, while the deletion of two nucleotides in kdpD leads to a fusion protein of KdpD with KdpE that inhibits the transcriptional activity of KdpE. Neither mutation led to hypervirulence in a mouse infection model. These results point to the role of other MDR B0/W148 specific mutations in the wide geographic diffusion of this clone and/or put in question a hypothesized hypervirulence as a driving factor for this large dissemination.
IMPORTANCE: Human tuberculosis (TB), caused by the bacterium Mycobacterium tuberculosis, remains a global public health issue estimated to have been responsible for 1.25 million deaths in 2023. Multidrug-resistant (MDR) strains of M. tuberculosis, resistant to rifampicin and isoniazid, lead to lower treatment success. Among them, the MDR B0/W148 clone has widely disseminated in Russia and Europe. To get more insights into the genetic factors underlying the evolutionary success of this clone, we investigated two strain-specific mutations found in the transcriptional regulators WhiB6 and KdpDE. By constructing and analyzing laboratory M. tuberculosis strains carrying these specific mutations, we found numerous changes in their transcriptional profiles, whereas we observed only a little impact of these mutations on the virulence of M. tuberculosis in a mouse infection model. Our study provides new insights into the transcriptional landscape of the selected MDR strains, although no direct connection to virulence could be established.

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PMID: 40401952

35. An Update on the Clinical Management of HIV and Tuberculosis Co-Infection in Pregnancy: TB Preventative Therapy, Long-Acting ARVs, and Bedaquiline-Based Regimens.

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Crocker-Buque T(1)(2), Moso MA(1)(2), Denholm JT(1)(2)(3), Singh KP(4)(5).

Author information:
(1)Department of Infectious Diseases, Peter Doherty Institute of Infection and Immunity, The University of Melbourne, Melbourne, VIC, Australia.
(2)Victorian Infectious Diseases Service, The Royal Melbourne Hospital, Melbourne, Australia.

(3)Victorian Tuberculosis Program, The Royal Melbourne Hospital, Melbourne, Australia.
(4)Department of Infectious Diseases, Peter Doherty Institute of Infection and Immunity, The University of Melbourne, Melbourne, VIC, Australia. kasha.singh@unimelb.edu.au.
(5)Victorian Infectious Diseases Service, The Royal Melbourne Hospital, Melbourne, Australia. kasha.singh@unimelb.edu.au.

PURPOSE: This update addresses HIV/TB co-infection management in pregnancy, focusing on new treatment options.
RECENT FINDINGS: Pregnancy with HIV increases TB risk and worsens treatment outcomes. While long-acting antiretroviral therapies (LA-ART) like cabotegravir/rilpivirine and lenacapavir exist, data on their safety and efficacy in pregnant individuals are limited. Treating both HIV and TB is crucial, but pregnancy's physiological changes complicate drug management. Standard ART and TB preventive therapy (TPT) with isoniazid are recommended after excluding active TB, despite some concerns about adverse outcomes when combined with ARV treatment. For active drug-resistant TB, the new 6-month BPaLM regimen (bedaquiline, pretomanid, linezolid, moxifloxacin) is not recommended in pregnancy due to limited safety data on pretomanid. Instead, a 9-month regimen is preferred, though bedaquiline and pretomanid are likely safe. More research on these new therapies in pregnant populations is needed. While standard ART remains the recommended approach for HIV/TB co-infection in pregnancy, further research is crucial to establish the safety and efficacy of newer LA-ART and bedaquiline-based TB regimens in this high-risk population. Concerns around the safety of TPT in pregnancy remain unanswered and further prospective research is urgently needed.

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PMID: 40522414 [Indexed for MEDLINE]

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36.Magnitude, predictors, and trends of multidrug-resistant tuberculosis among tuberculosis patients at Debre Markos, Northwest, Ethiopia: a five-year retrospective study.

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eCollection 2025 Jun.

Atnaf A(1), Kibret M(2), Tesfaye B(3), Abebaw D(1).

Author information:
(1)Department of Medical Laboratory Sciences, Debre Markos University, PO. Box 269, Debre Markos, Ethiopia.
(2)School of Medicine, Debre Markos University, PO. Box 269, Debre Markos, Ethiopia.
(3)Department of Nursing, Debre Markos University, PO. Box 269, Debre Markos, Ethiopia.

BACKGROUND: The emergence of multidrug-resistant tuberculosis (MDR-TB) is a threat to the people of resource-limited countries, such as Ethiopia. This study aimed to assess the magnitude, predictors and trends of multidrug-resistant tuberculosis among patients with pulmonary tuberculosis (TB) at Debre Markos Comprehensive and Specialized Hospital (DMCSH), Northwest Ethiopia.
MATERIALS AND METHODS: A retrospective cross-sectional study was conducted among patients with TB treated at the directly observed treatment short course (DOTS) clinic at DMCSH from 1 June 2016 to 1 June 2020. Data from 1509 patients with TB registered in the clinic were retrieved from medical records. Statistical analysis was performed using SPSS v.24. The frequency of variables is presented via tables and figures. Logistic regression was fitted to predictors of MDR-TB, and a P value <0.05 was considered statistically significant.
RESULTS: Overall, data from 1509 patients with pulmonary TB were retrieved during the study. The overall prevalence of MDR-TB was 4.1%. Variables such as sex, human immunodeficiency virus (HIV) status, lesion on chest X-ray, and a history of anti-TB treatment were significantly associated with MDR-TB. The trend of MDR-TB decreased by 40% in 2017, 29% in 2018, and 10% in 2019, but increased by 21% in 2020.
CONCLUSIONS AND RECOMMENDATIONS: The prevalence of MDR-TB among patients with pulmonary TB was comparable to the national rate. Key risk factors for MDR-TB included male sex, prior TB treatment, HIV infection, and chest X-ray abnormalities. The increasing trend in 2020 highlights the need for strengthened TB treatment adherence counselling and further prospective studies to explore additional predictors of MDR-TB.

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PMCID: PMC12107240
PMID: 40433447

37.Adverse drug reactions in persons initiated on treatment for drug-resistant tuberculosis in Kerala, India: A non-concurrent cohort study.

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Vaman RS(1)(2), Thomas GD(3), Kalyanasundaram M(4), Soman S(5), Valamparampil MJ(5), Puroshothama Bhat Susheela R(6), Murhekar MV(4).

Author information:
(1)District Hospital, Kanhangad, India.
(2)FETP-MPH programme, ICMR-NIE, Chennai, India.
(3)MOSC Medical College, Kolenchery, India.
(4)ICMR-NIE, Chennai, India.
(5)Kerala State Health Services, Thiruvananthapuram, India.
(6)The Union Southeast Asia Office, New Delhi, India.

OBJECTIVES: We conducted a study to estimate the incidence of adverse drug reactions (ADRs) in the drug-resistant tuberculosis (DR-TB) cohort in Kerala in 2020 and describe the characteristics of the reported ADRs.
METHODS: A non-concurrent cohort study was conducted among all patients with DR-TB across 14 districts in Kerala from January 1, 2020 to December 31, 2020. We collected data on ADRs from patients, "Nikshay" web-portal, treatment cards, case sheets, and registers. We described ADRs by organ system, causality, severity, preventability, predictability, and seriousness of the reaction using standard tools.
RESULTS: Of the 364 persons initiated on treatment, 304 (83.5%) had at least one of the 28 listed adverse reactions, with an incidence of 27.6 ADR per 100 person-months of treatment. Gastrointestinal disorders had the highest incidence 365 per 1046 (35%). A total of 1001 of 1046 (95.7%) ADRs were non-predictable, and 405 of 1046 (39%) were definitely preventable. A total of 83 of 304 (27.3%) patients had severe ADR, and 56 of 304 (18.4%) had serious ADR. A total of 87 of 304 (28.6%) patients with ADR required interruption of the probable offending drug, with 64 of 87 (73.6%) temporary and 23 of 87 (26.4%) permanent interruptions.
CONCLUSIONS: Four-fifths of all patients on therapy had at least one of the 28 listed adverse reaction and one-fifth had serious ADR. ADRs can lead to treatment interruptions. Early detection and prompt management is essential for improving treatment outcomes in patients with DR-TB.

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

38.Household economic burden and catastrophic expenditures in non-resistant tuberculosis patients: cross-sectional survey in Guizhou, China.

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Ma X(1), Huang A(1), Chen H(1), Zhou J(1), He Y(1), Wang W(2), Du R(2), Guo X(2), Zhao Q(2), Li J(1).

Author information:
(1)Guizhou Provincial Center for Disease Control and Prevention, Guiyang, China.
(2)School of Public Health, Fudan University, Shanghai, China.

OBJECTIVES: In accordance with the World Health Organization (WHO)'s "End TB Strategy," which aims to eradicate catastrophic expenditures faced by TB-affected families, we intend to thoroughly investigate and comprehend the economic burden, catastrophic expenditures, and contributing factors pertaining to non-drug-resistant tuberculosis patients' families in Guizhou Province. Our goal is to formulate policy recommendations that can effectively alleviate the financial strain on these patients and their families.
METHODS: The pulmonary tuberculosis cases, which were non-drug-resistant, registered across the province during May-June 2020, and successfully treated at the time of the survey, underwent questionnaire interviews conducted through probability proportional sampling. Utilizing the WHO methodology, the household economic burden borne by these patients was computed, with the mean and median (interquartile range), abbreviated as "M (IQR)," employed to describe the economic burden, and the proportion (%) used to depict catastrophic expenditures. Further analysis of the factors influencing catastrophic expenditures within these families was conducted using chi-squared (χ 2) tests and binary logistic regression.
RESULTS: The average total out-of-pocket expenses (OOP) incurred by 2,283 non-drug-resistant pulmonary tuberculosis patients in Guizhou Province amounted to 10,581.82 RMB ($1453.11), with a median expenditure of 5,277 RMB (IQR: 2,110-12,352 RMB). Notably, indirect expenses comprised 58.07% of the total expenditure. Taking the time of diagnosis as the cut-off point, the majority of these expenses occurred during the treatment phase, but the before diagnosis

stage also imposed a significant economic burden, averaging 3,191.58 RMB ($438.27). Among the 2,283 patients, 50.37% (1,150 patients) experienced catastrophic events due to their medical expenses. Key risk factors for these catastrophic events included poverty, employment status, before diagnosis visits, hospitalization, mobility issues, and delayed diagnosis.
CONCLUSION: The economic burden imposed on households by tuberculosis patients in the province remains considerable, with the indirect burden accounting for the lion's share. The likelihood of catastrophic expenditures persists, significantly influenced by factors such as poverty, hospitalization, delayed diagnoses, and before diagnosis visits. Recommendations include reinforcing targeted public health education, enhancing the diagnostic and therapeutic capabilities of medical institutions, regulating their practices, curbing unnecessary hospitalizations, and instituting a long-term framework aimed at alleviating the indirect economic burden. By doing so, we can collaboratively diminish the economic strain on patients and mitigate the risk of catastrophic expenditures, ultimately striving for the achievement of zero catastrophic expenditures among households.

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

39.Implementing active surveillance for tuberculosis: A quality improvement Project.

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Ajudua FI(1), Mash R.

Author information:
(1)Division of Family Medicine and Primary Care, Faculty of Medicine & Health Sciences, Stellenbosch University, Cape Town, South Africa; Department of Family Medicine and Rural Health, Faculty of Health Sciences, Walter Sisulu University, Mthatha, South Africa; and Department of Family Medicine, Faculty of Health Sciences, Nelson Mandela University, Gqeberha. febijudus@gmail.com.

BACKGROUND: South Africa is a high tuberculosis (TB)-burden country with the

worst multidrug-resistant TB (MDRTB) epidemic in Sub-Saharan Africa. The recommendations of the World Health Organization (WHO) in high TB-burden settings are to institute processes for identifying patients with active TB and to improve social support. The community-oriented primary care (COPC) model relies on the community health workers' (CHW) every encounter in the community as an opportunity to screen for TB symptoms. This study aimed to evaluate the implementation of active surveillance for TB in a CHW team.
METHODS: This was a quality improvement project (QIP) focused on the implementation of TB screening in the community-based services at a primary care facility in the Nelson Mandela Bay Health District (NMBHD).
RESULTS: The baseline audit revealed one team was available in the facility even though it serviced two and a half municipal wards. The team comprised an outreach team leader and three CHWs. There were no records of community-based TB screenings done. The midway audit showed a remarkable rise in clients screened in the community. There was a failed attempt to introduce the use of mHealth technology to the team. The audit at the end of the QIP showed a continuing lack of adequate records of activities in the community.
CONCLUSION: The CHWs in this study, although capable and motivated, lacked opportunity to perform adequate community-based TB screening because of the lack of supportive supervision, inadequate recordkeeping, and a district managerial team that focused on the practice population rather than the population at risk.Contribution: We recommend a continuing QIP and a re-education of health care providers about community-based health services.

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PMID: 40459118 [Indexed for MEDLINE]

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40. Resistance characteristics of culture-positive tuberculosis from 2015 to 2022.

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Wang Z(1)(2), Xu L(2)(3), Guo T(1), Li L(1), Zhang Q(1), Liu J(1), Zu X(2), Zhao Z(4), Xue Y(2).

Author information:
(1)The First Affiliated Hospital, College of Clinical Medicine of Henan University of Science and Technology, Luoyang, China.

(2)School of Medical Technology and Engineering, Henan University of Science and Technology, Luoyang, China.
(3)Clinical Laboratory Management Center, Luoyang Center for Disease Control and Prevention, Luoyang, Henan, China.
(4)College of Animal Science and Technology, Henan University of Science and Technology, Luoyang, China.

INTRODUCTION: This study aimed to investigate the prevalence of resistance to first-line anti-tuberculosis (TB) drugs and the molecular mechanisms underlying resistance mutations in patients with culture-positive Mycobacterium tuberculosis complex (MTBC). The findings provide a data basis for developing more precise and regionally tailored anti-TB treatment regimens.
METHODS: From 2015 to 2022, a total of 3,605 strains isolated from 10 designated TB medical institutions in the main urban and county/township areas of Luoyang City, China, were confirmed as MTBC members through polymerase chain reaction (PCR) targeting a specific insertion sequence IS6110. Drug susceptibility testing using the proportional method was performed to analyze resistance patterns to first-line anti-TB drugs, namely, isoniazid (INH), rifampin (RFP), streptomycin (SM), and ethambutol (EMB). Molecular drug susceptibility testing was conducted on resistant strains using multicolor melting curve analysis (MMCA) to determine the mutation mechanisms associated with phenotypic resistance.
RESULTS: Among the 3,605 culture-positive MTBC cases, 79.5% (2,866 cases) were male, 64.9% (2,341 cases) resided in county and township areas, and 64.8% (2,336 cases) were younger than 60 years. The resistance rates for first-line anti-TB drugs, from highest to lowest, were SM (16.5%), INH (15.7%), RFP (9.9%), and EMB (6.4%). The overall TB resistance rates were significantly higher in the main urban areas. During the study period, the proportion of mono-resistance tuberculosis (MR-TB), multidrug-resistant tuberculosis (MDR-TB) and polydrug-resistant tuberculosis (PDR-TB) decreased by 59.2% (12.9-5.3%), 40.3% (12.4-7.4%), and 68.3% (6.9-2.2%), respectively. The predominant resistance patterns for MDR-TB and PDR-TB were MDR4 (INH + RIF + EMB + SM) and PDR2 (INH + SM). The significant molecular mutations observed were rpsL43 for SM resistance (66.2%, 344 cases), katG315 for INH resistance (70.6%, 361 cases), rpoB529-533 for RFP resistance (54.0%, 183 cases), and embB306 for EMB resistance (56.5%, 108 cases). Resistance in MDR-TB and PDR-TB cases frequently involved combinations of hotspot mutations but was not strictly confined to these sites.
CONCLUSION: Tuberculosis resistance rates have declined over time, with distinct regional variations in resistance patterns. Significant molecular mutations responsible for drug resistance predominantly involve common hotspot mutations, but they are not limited to these.

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

41. Population pharmacokinetics and dosing of dispersible moxifloxacin formulation in children with rifampicin-resistant tuberculosis.

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Palmer M(1), Zou Y(2), Hesseling AC(1), van der Laan L(1), Courtney I(1), Kinikar AA(3), Sonkawade N(3), Paradkar M(4)(5), Kulkarni V(4)(5), Casalme DJO(6), Frias MVG(6), Draper H(1), Wiesner L(7), Karlsson MO(2), Denti P(7), Svensson EM(2)(8), Garcia-Prats AJ(1)(9).

Author information:
(1)Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Stellenbosch University, Cape Town, South Africa.
(2)Department of Pharmacy, Uppsala University, Uppsala, Sweden.
(3)B.J. Government Medical College, Pune, India.
(4)BJ Government Medical College-Johns Hopkins University Clinical Research Site, Pune, India.
(5)Center for Infectious Diseases in India, Johns Hopkins India, Pune, India.
(6)De La Salle Health Sciences Institute, Dasmarinas, The Philippines.
(7)Division of Clinical Pharmacology, Department of Medicine, University of Cape Town, Cape Town, South Africa.
(8)Department of Pharmacy, Radboud University Medical Center, Nijmegen, The Netherlands.
(9)Department of Pediatrics, University of Wisconsin-Madison, Madison, Wisconsin, USA.

AIMS: Moxifloxacin is a priority drug for treating rifampicin-resistant tuberculosis (RR-TB). We assessed the pharmacokinetics of a child-friendly, dispersible 100 mg tablet moxifloxacin formulation (dispersed in water) compared to the standard 400 mg non-dispersible formulation (crushed and suspended in water) in children and evaluated current dosing recommendations.
METHODS: The CATALYST trial investigated the pharmacokinetics of moxifloxacin in children with RR-TB. Children were enrolled in South Africa, India and the Philippines. Intensive pharmacokinetic sampling was undertaken while children were taking the standard non-dispersible 400 mg moxifloxacin tablet formulation

and repeated after switching to the novel dispersible formulation.
Pharmacokinetic data were analysed using population pharmacokinetic modelling. Simulations were performed to evaluate moxifloxacin exposures in children compared to consensus adult reference exposures using current World Health Organization (WHO)-recommended doses and more recent model-based doses.
RESULTS: Thirty-six children were enrolled [median age 4.8 (range 0.4-15) years and weight 15.6 (range 6.9-42.1) kg]. A two-compartment disposition model with first-order elimination and delayed absorption was developed. The bioavailability of dispersible versus standard formulations fulfilled standard bioequivalence criterion (ratio 1.05 with 90% confidence interval 0.95-1.15). Simulations showed WHO-recommended doses achieved exposures similar to those in adults in children >10 kg, while children <10 kg may require 33%-56% higher doses to reach adult reference exposures.
CONCLUSIONS: Dosing recommendations for children can be the same for the dispersible paediatric and standard non-dispersible adult moxifloxacin formulation. The current WHO dosing recommendation risks underdosing moxifloxacin in children <10 kg. We propose optimized moxifloxacin doses for both formulations.

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Conflict of interest statement: No conflicts of interest to declare.

42. DprE1 inhibitors: An insight into the recent developments and synthetic Approaches.

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Shahin MI(1), Elyamani MA(2), Elsawi AE(3), Negmeldin AT(4), Naguib S(2), Safwat H(2), Abdel-Aziz HA(5), Eldehna WM(6).

Author information:
(1)Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Ain Shams University, Abassia, Cairo 11566, Egypt.
(2)Scientific Research and Innovation Support Unit, Faculty of Pharmacy, Kafrelsheikh University, Kafrelsheikh, Egypt.
(3)Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Kafrelsheikh

University, Kafrelsheikh 33516, Egypt.
(4)Department of Pharmaceutical Sciences, College of Pharmacy and Thumbay Research Institute for Precision Medicine, Gulf Medical University, Ajman, United Arab Emirates; Department of Pharmaceutical Organic Chemistry, Faculty of Pharmacy, Cairo University, Cairo, Egypt. Electronic address: ahmed.n@pharma.cu.edu.eg.
(5)Department of Applied Organic Chemistry, National Research Center, Dokki, Cairo 12622, Egypt.
(6)Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Kafrelsheikh University, Kafrelsheikh 33516, Egypt; Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Pharos University in Alexandria; Canal El Mahmoudia St., Alexandria 21648, Egypt. Electronic address: wagdy2000@gmail.com.

In the current medical era, the proliferation and dissemination of drug-resistant strains of Mycobacterium tuberculosis (Mtb) continue to pose a significant worldwide health hazard, necessitating the development of new and innovative medications to combat tuberculosis. Decaprenylphosphoryl-β-D-ribose 2'-epimerase (DprE1) is a crucial enzyme for cell wall synthesis in Mtb. Its importance is due to its eminent contribution in forming lipoarabinomannan and arabinogalactan, key components of the mycobacterial cell wall. The emergence of the DprE1 enzyme as a druggable target was based on inhibitors discovered in high-throughput screening. Since then, inhibitors with different types of chemical scaffolds have been reported for their activity against it. DprE1 inhibitors can be categorized according to the formation of a covalent or non-covalent bond in the enzyme's active site, causing a loss of its catalytic activity, leading to Mtb's demise. Herein, we describe diverse DprE1 inhibitors that have had anti-tubercular activity reported over the past fifteen years and till the present time.

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

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

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

Author information:
(1)Department of Infectious Diseases, Wenzhou Central Hospital, The Dingli Clinical College of Wenzhou Medical University, Wenzhou, China.
(2)Laboratory of Infectious Diseases, Wenzhou Central Hospital, The Dingli Clinical College of Wenzhou Medical University, Wenzhou, China.
(3)Engineering Research Centre of Molecular Diagnostics of the Ministry of Education, State Key Laboratory of Cellular Stress Biology, School of Life Sciences, Faculty of Medicine and Life Sciences, Xiamen University, Xiamen, Fujian, China.
(4)Engineering Research Centre of Molecular Diagnostics of the Ministry of Education, State Key Laboratory of Molecular Vaccinology and Molecular Diagnostics, School of Life Sciences, Faculty of Medicine and Life Sciences, Xiamen University, Xiamen, Fujian, China.
(5)Department of Tuberculosis Control and Prevention, Zhejiang Provincial Center for Disease Control and Prevention, Hangzhou, China.
(#)Contributed equally

Resistance to pyrazinamide (PZA) poses significant challenges to tuberculosis (TB) management, and prediction of susceptibility to PZA has been challenging. This study examined PZA resistance-associated gene mutations in 125 multidrug-resistant clinical isolates of Mycobacterium tuberculosis (MTB) from Wenzhou, China. Phenotypic drug-susceptibility testing (pDST) for PZA was performed on clinical isolates using the MGIT 960 system to accurately determine resistance. Subsequently, whole-genome sequencing (WGS) was conducted on the 125 isolates to identify genetic mutations linked to PZA resistance, focusing specifically on the pncA, rpsA, and panD genes. To provide a rapid diagnostic alternative to traditional methods, the MeltPro MTB/PZA assay was also utilized to detect mutations in pncA. pDST revealed a PZA resistance rate of 59.20%, with 29.41% observed in strains resistant only to isoniazid and rifampicin, 77.61% in pre-extensively drug-resistant TB (pre-XDR-TB), and 100% in extensively drug-resistant TB (XDR-TB). Among the isolates, WGS identified mutations primarily in the pncA (64.00%) and rpsA (6.40%), with panD mutations not detected. PZA resistance was strongly associated with pncA mutations, present in 97.30% of PZA-resistant strains. WGS demonstrated 97.30% sensitivity and 84.31% specificity compared to pDST, while MeltPro MTB/PZA showed 91.89% sensitivity and 86.27% specificity. Compared to WGS, MeltPro MTB/PZA showed 92.50% positive percent agreement and 97.78% negative percentage agreement, highlighting its diagnostic value. In conclusion, PZA resistance in multidrug-resistant tuberculosis (MDR-TB) is primarily due to pncA mutations. MeltPro MTB/PZA assay offers a reliable, rapid alternative for PZA resistance prediction, supporting timely treatment adaptations for improved TB patient care.

IMPORTANCE: This study underscores the pressing need for reliable diagnostic methods to address high PZA resistance rates in TB cases, particularly in MDR-TB strains. By confirming that pncA mutations are the principal drivers of PZA resistance, we highlight the diagnostic potential of the MeltPro MTB/PZA assay as a rapid and effective alternative to conventional culture-based methods. Demonstrating sensitivity and specificity comparable to WGS and pDST, this assay offers a practical, accessible approach for timely PZA resistance prediction. It supports more tailored and effective MDR-TB treatment strategies, which are essential for optimizing patient care in both well-resourced and constrained settings.

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PMID: 40401978

44. A comprehensive evaluation of a novel targeted-sequencing workflow for Mycobacterium species identification and anti-tuberculosis drug-resistance Detection.

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Ou X(#)(1), Pei S(#)(1)(2), Li H(#)(3), Qin Z(#)(4), Anthony R(5), Wang J(6), Song Z(1), Xing R(1), Zhang L(4), Teng C(7), Xia H(1), Zhou Y(1), Song Y(1), Zheng Y(1), Wang S(1), Zhao B(1), Zhao Y(1).

Author information:
(1)National Key Laboratory of Intelligent Tracking and Forecasting for Infectious Diseases, National Center for Tuberculosis Control and Prevention, Chinese Center for Disease Control and Prevention, Beijing, China.
(2)School of Public Health, Peking University, Beijing, China.
(3)Department of Neurology, The First Affiliated Hospital of Anhui Medical University, Hefei, China.
(4)Center for Accurate Detection of Tuberculosis, Tianjin Haihe Hospital, Tianjin, China.
(5)Centre for Infectious Disease Control, National Institute for Public Health and the Environment, Bilthoven, Netherlands.
(6)Department of Science and Technology, Chinese Center for Disease Control and Prevention, Beijing, China.
(7)Department of Tuberculosis, Beijing Dongcheng District Center for Disease Control and Prevention, Beijing, China.
(#)Contributed equally

BACKGROUND: Although several World Health Organization-endorsed targeted

next-generation sequencing (tNGS) assays exist for tuberculosis (TB) drug-resistance detection, their target selection and diagnostic accuracy vary widely. In this study, we developed a novel tNGS workflow (the TB Pro assay) and evaluated its performance in identifying Mycobacterium species and predicting drug resistance.
METHODS: The TB Pro assay was validated for identifying 10 Mycobacterium tuberculosis complex (MTBC) and 39 nontuberculous mycobacterial (NTM) species, as well as predicting resistance to 4 first-line and 13 second-line anti-TB drugs. The limit of detection (LOD) was determined using 11 reference strains spiked in sputum. The prediction of resistance to anti-tuberculous drugs/drug classes was compared with phenotypic drug susceptibility testing (pDST) and whole-genome sequencing (WGS) using 435 clinical isolates.
RESULTS: The assay demonstrated high sensitivity with a calculated LOD of 3.0 CFU/ml for MTB and 1.4-16.2 CFU/ml for most NTMs, except for Mycobacterium intracellulare with 117.9 CFU/ml. Using pDST as the reference standard, the sensitivity of the TB Pro assay for the detection of resistance ranged from 74.3% (ethambutol) to 94.4% (rifampicin), with specificity values >98% for all drugs. Compared with WGS, the sensitivity of the TB Pro assay was over 98.0% for all drugs except pyrazinamide (66.7%), and the specificity values were all nearly 100.0%. Directly on sputum, the TB Pro assay showed 100% agreement with smear- and culture-positive sputum specimens.
CONCLUSIONS: The TB Pro assay represents a sensitive and specific solution for simultaneous mycobacterial identification and comprehensive drug-resistance profiling, performing robustly on both cultured isolates and direct clinical specimens.

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PMID: 40552123 [Indexed for MEDLINE]

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

45. Comparative study on the virulence of mycobacteriophages.

J Virol. 2025 Jun 17;99(6):e0192024. doi: 10.1128/jvi.01920-24. Epub 2025 May 21.

Rubino I(1)(2), Guerrero-Bustamante CA(3), Harrison M(1), Co S(1), Tetreau I(4),

Ordoubadi M(4), Larsen SE(5), Coler RN(5)(6)(7), Vehring R(4), Hatfull GF(3), Sauvageau D(1).

Author information:
(1)Department of Chemical and Materials Engineering, University of Alberta, Edmonton, Alberta, Canada.
(2)Department of Chemical and Biotechnological Engineering, Université de Sherbrooke, Sherbrooke, Québec, Canada.
(3)Department of Biological Sciences, University of Pittsburgh, Pittsburgh, Pennsylvania, USA.
(4)Department of Mechanical Engineering, University of Alberta, Edmonton, Alberta, Canada.
(5)Seattle Children's Research Institute, Center for Global Infectious Disease Research, Seattle, Washington, USA.
(6)Department of Pediatrics, University of Washington School of Medicine, Seattle, Washington, USA.
(7)Department of Global Health, University of Washington, Seattle, Washington, USA.

Update of
bioRxiv. 2024 Oct 29:2024.10.23.619922. doi: 10.1101/2024.10.23.619922.

The global tuberculosis (TB) epidemic affected 10 million people and caused 1.3 million deaths in 2022 alone. Multidrug-resistant TB is successfully treated in less than 60% of cases by long, expensive, and aggressive treatments. Mycobacteriophages, viruses that can infect bacteria such as Mycobacterium tuberculosis-the species responsible for TB-have the potential to redefine TB prevention and treatments. However, the development of phage-based products necessitates the assessment of numerous parameters, including virulence and adsorption, to ensure their performance and quality. In this work, we characterized the virulence of three different mycobacteriophages (Fionnbharth, Muddy, and D29), alone and as cocktails, against a TB model host (Mycobacterium smegmatis) under planktonic and early-stage biofilm growth conditions. Phage D29 and cocktails containing D29 had the highest virulence under all conditions. Interestingly, phages Fionnbharth and Muddy and their combination showed higher virulence against early-stage biofilm than against the planktonic phenotype. Adsorption assays indicated that all three phages had lower adsorption efficiencies on the early-stage biofilm phenotype than on the planktonic one, suggesting a reduced availability of receptors in the former. Given that, despite these lower adsorption efficiencies, the virulence of the phages and phage cocktails was either unchanged or higher against the early-stage biofilm, this phenotype must display properties that are favorable to other steps of the infection process. These results inform us on the dynamics of mycobacteriophage infections, both alone and in cocktail formulations, under different host growth

conditions, serving as a basis for the development of phage products targeting mycobacteria biofilms.
IMPORTANCE: This study provides a systematic investigation of the virulence of three mycobacteriophages, Fionnbharth, Muddy, and D29, and their combinations as cocktails against Mycobacterium smegmatis. We also included considerations on the hydrodynamic conditions (shaking and not shaking) and host phenotype (planktonic and early-onset biofilm cultures) during the infection process and adsorption of the phage to the host. We showed that virulence was strongly affected by phenotype and that higher virulence shown against the early-onset biofilm phenotype was not linked to faster adsorption to the host. We also showed that phage D29 and cocktails containing this phage had the highest virulence. These results are important as they provide a framework for a better evaluation and development of phage-based treatment against mycobacterial infections.

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46. Discrepancies in tuberculosis burden estimates: North Korean defectors vs. official reports.

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Jang I(#)(1), Han H(#)(1), Lee S(2), Jeong H(2), Lee R(2), Kang Y(3), Oh IH(#)(4), Lee SH(#)(3)(5).

Author information:
(1)College of Medicine, Korea University, Seoul, Republic of Korea.
(2)Department of Preventive Medicine, Kyeong Hee University School of Medicine, Seoul, Republic of Korea.
(3)Division of Pulmonology, Sleep and Critical Medicine, Department of Internal Medicine, Korea University Ansan Hospital, Ansan, Republic of Korea.
(4)Department of Preventive Medicine, University of Ulsan College of Medicine, Seoul, Republic of Korea.
(5)Ansan Central Internal Medicine, Ansan, Republic of Korea.
(#)Contributed equally

OBJECTIVES: North and South Korea have taken different approaches to tuberculosis (TB) epidemic control after the Korean War. This study aimed to

compare TB epidemiology in North Korean defectors (NKDs) based on South Korean National Health Insurance (NHIS) data and assess its implications for understanding TB prevalence in North Korea.
METHODS: We used the NHIS claims data from 2007 to 2019 to evaluate TB epidemics in NKD and the age-and-sex matched South Korean control group. The number of participants was 35,620 for defectors and 107,016 for the control group.
RESULTS: The prevalence of TB among NKDs decreased from 466/100,000 persons in 2010 to 95/100,000 persons in 2019, while the North Korean TB prevalence as per the World Health Organization (WHO) report remained approximately 500/100,000 persons. The NKD TB prevalence was 3-7 times higher than that in the South Korean population. Additionally, the distribution of TB cases in NKDs showed distinct age-related patterns, with peaks in the 25-34 and 65 + age groups. The proportion of extrapulmonary TB in NKDs was 36-46%, similar to South Korean patterns. The estimated and reported multidrug-resistant TB rates in NKDs were higher than in the control group, highlighting potential underreporting in North Korean data.
CONCLUSION: There were large gaps in TB prevalence between NKD and native North Korean residents and between the estimated and reported TB burden within North Korea. These findings underscore the need for targeted TB control strategies that address both health system disparities and the integration of NKDs into local healthcare services.

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47. The role of stakeholder mapping and engagement in Mongolia during the implementation of the STREAM clinical trial for MDR-TB.

Trials. 2025 May 29;26(1):179. doi: 10.1186/s13063-025-08887-7.

Tsogt B(1)(2), Gurumurthy M(3), Giallongo E(4), Sanders K(4), Munkhjargal G(5)(6), Khukhuukhen Z(7), Bolormaa E(6), Raash E(6), Nyamdavaa N(5), Bronson G(8).

Author information:
(1)National Center for Communicable Diseases, Ulaanbaatar, Mongolia. bazra.ts@outlook.com.
(2)Mongolian Anti-TB Coalition, Ulaanbaatar, Mongolia. bazra.ts@outlook.com.
(3)Vital Strategies Health Systems, Asia Pacific, Singapore, Singapore.
(4)Medical Research Council Clinical Trials Unit at UCL, London, England.
(5)Mongolian Anti-TB Coalition, Ulaanbaatar, Mongolia.
(6)Community Advisory Board, Ulaanbaatar, Mongolia.
(7)National Center for Communicable Diseases, Ulaanbaatar, Mongolia.
(8)Vital Strategies, New York, USA.

BACKGROUND: Clinical trials evaluating new regimens for multidrug-resistant tuberculosis (MDR-TB) are typically conducted in multiple countries because global registration of new TB drugs requires evaluation in diverse populations. The complexity of multi-site trials makes implementation challenging, especially in lower-resource settings, where the burden of MDR-TB is highest. Stakeholder engagement can improve trial implementation and outcomes. Here, we describe the Mongolia site's stakeholder engagement during STREAM, a phase III clinical trial evaluating novel treatment regimens for MDR-TB.
MAIN BODY: We assessed our stakeholder engagement against the PCORI rubric. Engagement at all phases of the trial aligned well with the PCORI engagement principles of reciprocal relationships; co-learning; building partnerships; and transparency, honesty, and trust. In the planning phase, we formed a key partnership with a civil society organization to co-lead the trial, undertook stakeholder mapping, and developed an overall engagement strategy. During trial implementation, we undertook activities aimed at ensuring feasibility of the study, improving recruitment, ensuring viability of the study, and ensuring authenticity/value of stakeholder engagement. Activities, which included continuous communication with the national TB program to ensure referral of potential trial participants, implementation of a comprehensive community engagement (CE) program, delivery in collaboration with partners of psychosocial support for trial participants, capacity-building and knowledge sharing, regular communications on trial developments and progress, and community advisory board (CAB) participation in CE assessment, contributed to achieving a 98% retention rate and the highest participant recruitment across all STREAM trial sites. In the dissemination phase, CAB members worked together with the site and sponsor to ensure strategies and materials were tailored to stakeholders' needs, including participants; communities; frontline healthworkers; and national-level stakeholders. Stakeholder participation in research and in improving routine TB care in the country has been sustained since completion of the trial.
CONCLUSIONS: Significant and sustainable gains can be made through stakeholder collaboration. We recommend that trial sites in lower-resourced settings take an expansive view of relevant stakeholders when planning engagement; undertake capacity-building and knowledge sharing; plan for long-term sustainability of

CE; design engagement around specific objectives; tailor and optimize communication strategies; and design stakeholder engagement to involve key policy makers.
TRIAL REGISTRATION: ISRCTN78372190 - Registration date is October 14, 2010 (Stage 1) and ISRCTN18148631 - Registration date is February 10, 2016 (Stage 2).

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48.Population pharmacokinetic and exposure-response study of a novel anti-tuberculosis drug to inform its dosage design in phase III clinical trial.

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Kong W(1), Liang H(1), Zhang Y(2), Li L(3), Li Y(3), Yan X(4), Liu D(5).

Author information:
(1)Drug Clinical Trial Center, Peking University Third Hospital, Beijing, PR China; Department of Nephrology, Peking University Third Hospital, Beijing, PR China.
(2)Drug Clinical Trial Center, Peking University Third Hospital, Beijing, PR China.
(3)Shanghai Jiatan Biotech Ltd., a subsidiary of Guangzhou JOYO Pharma Ltd., Shanghai, PR China.
(4)School of Pharmacy, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR, PR China. Electronic address: xiaoyuyan@cuhk.edu.hk.
(5)Drug Clinical Trial Center, Peking University Third Hospital, Beijing, PR China; Institute of Medical Innovation, Peking University Third Hospital, Beijing, PR China. Electronic address: liudongyang@vip.sina.com.

Although bedaquiline (BDQ) received conditional approval for multi-drug resistance tuberculosis (MDR-TB), a black box warning was added due to QT prolongation risk. WX-081, a promising second-in-class drug that finished phase II clinical trial, exhibited comparable anti-TB activity and better cardiac safety. The accumulation of its active metabolite WX-081-M3 leads to QT

prolongation, whereas the relationships between dosage, exposure and response have not been established. Accordingly, the dosage design for phase III study is challenging. Here, the first population pharmacokinetic (PPK) and exposure-response (E-R) analysis were conducted for WX-081. 1610 WX-081 and 1580 WX-081-M3 concentrations were collected from 24 healthy volunteers and 48 tuberculosis patients for PPK study. The pharmacokinetic parameters and sputum culture conversions of 20 MDR-TB patients receiving BDQ and WX-081 were used for E-R analysis. The absorption of WX-081 was well described by a three-compartments transit model, while the distribution and elimination profiles of WX-081 and WX-081-M3 were captured by three- and two-compartments models, respectively. E-R analysis demonstrated that the clinical efficacy of WX-081 is comparable with BDQ and can be evaluated by average concentration at steady state (Cavg,ss) of WX-081. According to the simulation results of different regimens, the dosage of 450 mg once daily (QD) for 1 week and subsequent 300 mg QD for 1 week followed by 150 mg QD for 22 weeks was recommended considering both efficacy and safety. Our study revealed the PK and efficacy profiles of WX-081 for the first time and proposed a dose optimization strategy to facilitate its clinical development.

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Conflict of interest statement: Declaration of competing interest Lei Li and Yongguo Li are employees of Shanghai Jiatan Biotech Ltd. All other authors declare no competing interests.

49.Habitat radiomics and transformer fusion model to evaluate treatment effectiveness of cavitary MDR-TB patients.

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Lv X(1), Wang Y(2), Ding C(3), Qin L(3), Xu X(1), Li Y(4), Hou D(1).

Author information:
(1)Department of Radiology, Beijing Chest Hospital, Capital Medical University, Beijing, China.
(2)Department of Radiology, Beijing Tuberculosis and Thoracic Tumor Research Institute, Beijing, China.
(3)Department of Radiology, Wuhan Pulmonary Hospital, Wuhan, China.
(4)Department of Radiology, Shandong Provincial Hospital Affiliated to Shandong

First Medical University, Shandong Provincial Hospital, Jinan, China.

Promptly identification of multidrug-resistant tuberculosis (MDR-TB) patients at high risk of treatment failure is essential for improving cure rates. This study aimed to develop a habitat radiomics based transformer fusion model to assess treatment effectiveness of MDR-TB. Independent patient cohorts from two hospitals were included. Radiomics features were extracted from the habitat and peripheral regions of cavities to construct predictive models. Then, a transformer-based fusion model integrating features from all regions was established. The areas under the receiver operating characteristic curves (AUCs) were used to evaluate the performance. The transformer fusion model combining two subregions and peripheral area achieved remarkable performance, with AUC values of 1.000, 0.959, and 0.879 in the training, validation, and test cohort, respectively. The finding highlights the efficacy of our model in predicting treatment effectiveness of MDR-TB patients and its potential to guide individualized therapy.

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PMID: 40546963

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

50. Time to reoccurrence of tuberculosis and its predictors among adult HIV/AIDS patients on ART at public hospitals in East and Horro Guduru Wollega zones, West Ethiopia: a retrospective cohort study.

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Feyisa JW(1), Dufera M(2), Feyisa BR(1)(3), Debelo S(1), Dori J(4), Shama AT(5).

Author information:
(1)School of Public Health, Institute of Health Sciences, Wollega University, Nekemt, P.O. Box: 395, Ethiopia.
(2)Department of Biology, College of Natural and Computational Sciences, Wollega University, Nekemt, Ethiopia.
(3)Department of Epidemiology, Faculty of Public Health, Jimma University, Jimma, Ethiopia.
(4)School of Nursing and Midwifery, Institute of Health Sciences, Wollega University, Nekemt, Ethiopia.
(5)School of Public Health, Institute of Health Sciences, Wollega University,

Nekemt, P.O. Box: 395, Ethiopia. adisuteferi1906@gmail.com.

BACKGROUND: The reoccurrence of Tuberculosis infection is one of the challenging problems in meeting the global Tuberculosis prevention goal. It contributes to morbidity and mortality, economic crisis, spread of infection among the population, and affects health-related quality of life. Despite the public health significance of the problem, there is a paucity of knowledge to well understand the time to reoccurrence of tuberculosis among HIV population and the factors that determine the recurrence of the problem in the context of Ethiopia.
OBJECTIVE: To assess the time to reoccurrence of tuberculosis and its predictors among adult HIV/AIDS patients attending ART clinics at health facilities in East and Horro Guduru wollega zones.
METHODS: A Hospital-based retrospective follow-up study was conducted among HIV/AIDS patients attending the ART clinic from Jan 1, 2015 to Feb, 30, 2020 by collecting information from the medical records of 442 patients. A sampling frame from the ART log book was prepared. A simple random sampling technique from patient records was employed. The structured checklist was used. Bivariable and multivariable Cox regression with crude hazard ratio and the adjusted hazard ratio, respectively, were used to identify independent predictors for the reoccurrence of Tuberculosis. A P-value of < 0.05 with 95% CI was used to declare significantly associated predictors.
RESULT: The median survival time of TB reoccurrence in this study was 72 months. Sex (AHR = 4.90 (95%CI:1.98, 12.53), widowed marital status (AHR = 4.00; 95%CI:1.13, 14.14), occupational status (AHR = 3.45;95%CI: 1.12, 10.64), advanced WHO clinical stages (AHR = 6.98; 95%CI: 1.71, 28.45), recurrence of opportunistic infections (AHR = 10.49; 95%CI:2.14, 51.54), low adherence to Anti-TB drugs (AHR = 2.38; 95%CI:1.01, 5.64), facing multidrug resistance during the preceding episode of TB (AHR = 25.06; 95%CI:6.49, 96.66), CD4 count < 200 (AHR = 10.09 95%CI: 3.62, 28.17), and viral load (AHR = 1.01 (95%CI:1.00, 1.02) were significant predictors of TB reoccurrence among HIV patients.
CONCLUSION: The median survival time among adult HIV patients was higher in the first 80 months of ART initiation and it decreased over the time of ART. Sex, occupational status, marital status, low CD4 count, viral load, advanced WHO clinical stage, reoccurrence of other opportunistic infections, poor adherence to TB treatment, and facing multidrug-resistant TB were independent predictors for reoccurrence of TB among HIV-positive adults.

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participate: This study was done in accordance with the Declaration of Helsinki. A letter of ethical clearance was obtained from the institutional research ethics review committee of Wollega University with reference number (IHSRPTTAD/147/2023). The ethics committee provided the approval for the waiver of informed consent from the participants as the secondary data were used. Data were collected after explaining to the institutional research ethics review committee that the confidentiality of record review was kept, and no exposition of data at individual level. Permission letter was taken from the East and Horro Guduru Wollega zonal health departments and hospital administrations. Consent for publication: Not applicable. Competing interests: The authors declare no competing interests.

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

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

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

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

in-depth studies on its mechanism and host immune-modulatory effects, necessitating further research before broad clinical adoption.

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

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

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

Rifampin (RIF) resistance in Mycobacterium tuberculosis (M.tb) is primarily caused by mutations in the rpoB gene. Rapid and accurate detection of RIF resistance is critical for effective tuberculosis (TB) control. Nucleotide matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) is an emerging technology used to detect RIF resistance-associated rpoB mutations in 210 M.tb clinical isolates, including 107 RIF-sensitive and 103 RIF-resistant strains, as determined by phenotypic drug susceptibility testing (DST). DNA sequencing was used as the reference method to validate nucleotide MALDI-TOF MS results. Nucleotide MALDI-TOF MS demonstrated a sensitivity of 93.2%, specificity of 98.1%, and an overall accuracy of 95.7% compared to phenotypic DST. The Kappa value between nucleotide MALDI-TOF MS and phenotypic DST was 0.91, indicating excellent agreement. DNA sequencing confirmed that nucleotide MALDI-TOF MS successfully identified RIF resistance-associated mutations, particularly in codons 450, 445, and 435 of the rpoB gene. Among the 61 isolates analyzed by DNA sequencing, nucleotide MALDI-TOF MS and sequencing results were consistent for 52 of 56 RIF-resistant strains and all five RIF-sensitive strains, with an overall concordance of

93.4%. Importantly, nucleotide MALDI-TOF MS accurately detected heteroresistance in eight isolates (14.3%), confirmed by sequencing. These results support that nucleotide MALDI-TOF MS is a rapid, accurate, and reliable method for detecting rpoB mutations associated with RIF resistance in M.tb. Its high concordance with DNA sequencing, excellent diagnostic performance, and ability to identify heteroresistance highlight its potential as a valuable tool for early TB diagnostics and improve the precision of chemotherapy regimen development.IMPORTANCEThe emergence of multidrug-resistant tuberculosis (MDR-TB) and rifampin-resistant tuberculosis (RR-TB) poses a significant challenge to global tuberculosis (TB) control efforts. Rifampin (RIF) resistance is a critical marker for MDR-TB, which requires more complex, prolonged, and costly treatment regimens. Early and accurate detection of RIF resistance is crucial for effective TB control. This study evaluates the performance of nucleotide MALDI-TOF MS, an innovative technology, for detecting RIF resistance-associated mutations in the rpoB gene. The method demonstrates high sensitivity (93.2%) and specificity (98.1%), with the added advantage of identifying heteroresistance, capabilities that are lacking in conventional methods. These capabilities are crucial for early diagnosis, guiding personalized treatment regimens, and curbing the transmission of drug-resistant TB. The findings demonstrate that nucleotide MALDI-TOF MS provides a rapid, high-throughput, and cost-effective alternative for detecting rpoB gene mutations associated with RIF resistance.

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53. Epidemiological Trends and Treatment Outcomes: Findings of a TB Survey From Selected Districts of Madhya Pradesh, India.

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Bhatia M(1), Sharma Y(2), Dwivedi V(3), Sukla P(1), Mitra B(1), Pandey V(4), Rai V(5).

Author information:
(1)Community Medicine, Government Medical College, Datia, Datia, IND.
(2)Community Medicine, World Health Organization Regional Office, Bhopal, IND.
(3)Community Medicine, Chhindwara Institute of Medical Sciences, Chhindwara, IND.
(4)Biostatistics, Government Medical College, Datia, Datia, IND.
(5)Tuberculosis and Infectious Diseases, State TB Task Force, Bhopal, IND.

BACKGROUND AND OBJECTIVE: Tuberculosis (TB) remains a significant public health

challenge in India, particularly in Madhya Pradesh. In this study, we aimed to examine epidemiological trends and treatment outcomes in TB patients in the Datia and Tikamgarh districts of Madhya Pradesh, from 2018 to 2022, to inform targeted TB control strategies.
METHODS: We conducted a retrospective observational study using data from the National TB Elimination Program (NTEP), accessed through the Nikshay portal (a Government of India initiative). We analyzed trends in TB notifications, rates of microbiological confirmation, treatment outcomes, and co-infections. Statistical tests, including the Mann-Whitney U test, Kruskal-Wallis test, and chi-square test, were employed, with a p-value of less than 0.05 indicating statistical significance.
RESULTS: In Datia, the proportion of pediatric TB cases decreased from 6% to 3% ($p = 0.04$), while extrapulmonary TB (EPTB) cases rose from 11.3% to 13.8% ($p = 0.02$). Notifications from the private sector significantly increased from 4% to 28% ($p = 0.03$), whereas drug-resistant TB (DR-TB) cases fell from 2% to 1% ($p = 0.02$). TB-related mortality rose from 3.28% to 3.93% ($p = 0.008$), with the proportion of patients lost to follow-up remaining stable at 9%-10% ($p = 0.02$). In Tikamgarh, pediatric TB rates declined from 7.7% to 6.3% ($p = 0.04$), and EPTB cases increased from 4.77% to 9.37% ($p = 0.02$). Notifications from the private sector surged from 1.13% to 20.75% ($p = 0.03$). DR-TB rates decreased from 4.33% to 1% ($p = 0.02$), but TB-related mortality increased from 1.87% to 5.46% ($p = 0.008$). The rate of patients lost to follow-up improved slightly, decreasing from 12.71% to 10.09% ($p = 0.02$).
CONCLUSION: The reduction in pediatric TB and DR-TB indicates progress in diagnosis and treatment adherence. However, the rising incidence of EPTB and increasing mortality rates highlight ongoing challenges. Enhancing private sector involvement, improving patient adherence, and integrating HIV-TB care are crucial for achieving India's TB elimination objectives.

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submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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

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

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

Tuberculosis (TB) returns to be the leading infectious killer globally after coronavirus disease 2019. The World Health Organization (WHO) formally included targeted next-generation sequencing (tNGS) in its list of recommendations for Mycobacterium tuberculosis (MTB) and drug resistance (DR). In this study, we explored the application of various clinical sample types for TB diagnosis and DR profiles. In comparison to the composite reference standard, the overall sensitivity values of culture, Xpert, metagenomic next-generation sequencing (mNGS), and tNGS were 0.458, 0.614, 0.772, and 0.760, respectively. tNGS had sensitivity similar to mNGS, which had advantages over culture and Xpert, respectively, despite different classification of sample types. In comparison to the microbiological reference standard, the overall sensitivity values of culture, Xpert, mNGS, and tNGS were 0.606, 0.811, 0.856, and 0.884, respectively. Suprisingly, in extrapulmonary tissue and serous effusion, mNGS and tNGS had advantages over Xpert. DR-related mutations were detected in 15 cases (13.2%). There were 51 (44.7%) applicable for all DR genes, with 22 (19.3%) not applicable for DR genes. DR genes were partially applicable in 41 (36.0%) samples. However, in culture-negative TB cases, tNGS can additionally provide 52.7% first-line DR profiles. Sanger sequencing was performed on 14

samples to confirm gene mutation identified by tNGS, and the results were entirely consistent. It was concluded that the tNGS assay was a promising approach in the initial diagnostic test of MTB and DR-related genes in different clinical samples, even for the smear- and culture-negative paucibacillary samples.IMPORTANCEtNGS combines gene-specific amplification with next-generation sequencing to detect MTB and drug-resistant genes by amplifying numerous loci directly from clinical samples. The WHO implemented tNGS for the purpose of monitoring respiratory specimens for MTB detection and DR-TB due to its high sensitivity and specificity, culture independence, and ability to report heterogeneous/silent mutations. The sensitivity outperformed both culture and Xpert, and the turnaround time was significantly less than that of culture-based assays. The tNGS assay used in this study costs USD 96 and has a 12 hour turnaround time. Nonetheless, tNGS has a great deal of promise for enhancing TB detection while also addressing DR strains.

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55. End of treatment and 12-month post-treatment outcomes in patients treated with all-oral regimens for rifampicin-resistant tuberculosis in Ukraine: a prospective cohort study.

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Fardhdiani V(1)(2), Trush O(1), Lytvynenko N(3), Pylypchuk S(3), Terleeva Y(4), Malakyan K(5), Rupasinghe P(6)(7), Wally Y(2), Duka M(1), Didyk VS(8), Siomak OV(8), Blyzniuk O(8), Furin J(9), Donchuk D(10), Laxmeshwar C(1)(11), Isaakidis P(10)(12).

Author information:
(1)Médecins Sans Frontières, Zhytomyr, Ukraine.
(2)Médecins Sans Frontières, Brussels, Belgium.
(3)National TB Institute, Kyiv, Ukraine.
(4)Department of TB Programme Coordination, Public Health Center of the MOH, Kyiv, Ukraine.
(5)Médecins Sans Frontières, Kyiv, Ukraine.
(6)Mycobacteriology unit, Department of Biomedical Sciences, Institute of Tropical Medicine, Antwerp, Belgium.
(7)Department of Biomedical Sciences, University of Antwerp, Antwerp, Belgium.
(8)Zhytomyr Regional TB Dispensary, Zhytomyr, Ukraine.
(9)Harvard Medical School, Cambridge, Massachusetts, United States of America.
(10)Southern Africa Medical Unit, Médecins Sans Frontières, Cape Town, South

Africa.
(11)Department of Global Health, University of Washington, Seattle, United States of America.
(12)Clinical and Molecular Epidemiology Unit, Department of Hygiene and Epidemiology, University of Ioannina School of Medicine, Ioannina, Greece.

The World Health Organization has called for operational research on all-oral shorter regimens for rifampin-resistant and multidrug-resistant forms of tuberculosis (RR/MDR-TB). We followed a cohort of patients in Zhytomyr, Ukraine for effectiveness, safety, tolerability and feasibility of bedaquiline & delamanid-based treatment regimens under programmatic conditions. This was a single-arm implementation study. All consenting persons with RR/MDR-TB were enrolled between 1 April 2019 and 31 May 2021 and followed up 12-months after treatment completion. We assessed quality of life and depression symptoms between start and end-of-treatment. We enrolled 300 patients. Overall, 212 (71%) patients were cured, 22 (7%) patients completed treatment, median time to culture conversion was 58 days (IQR:30-75), and 21% and 27% of patients had at least one serious or Grade 3/4 adverse event, respectively. The overall BREF-WHO/Quality of Life score improved between baseline and end-of-treatment, from average 52.64(std. dev:21.63) to 57.15(std. dev:21.43) while Patient Health Questionnaire-9(PHQ-9) score decreased from 6.67(std. dev:4.75) at baseline to 5.34(std. dev: 5.18) at end-of-treatment. Twelve months post-treatment 174/234(74%) were alive and recurrence-free, 17(7%) patients died, one (<1%) had recurrent TB, while 42 (18%) were lost from the post-treatment follow-up.
All-oral short-term regimens showed high success under programmatic conditions in Ukraine, despite extreme implementation challenges during the COVID-pandemic and the Russia-Ukraine war. Moreover, this was a cohort of patients with high levels of co-morbidities and substance use. A multidisciplinary, psychosocial support model might have contributed to satisfactory treatment outcomes, improved quality of life and decreased symptoms of depression among people living with RR/MDR-TB.

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DD, CL, and PI. This does not alter our adherence to PLOS Global Public Health policies on sharing data and materials. There are no patents, products in development, or marketed products associated with this research.

56.Resistance Rates of Mycobacterium tuberculosis Complex Strains: A Retrospective Study in Türkiye.

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Payaslıoğlu M(1), Sağlık İ(1), Özakın C(1).

Author information:
(1)Department of Medical Microbiology, Faculty of Medicine, Bursa Uludağ University, Bursa 16000, Turkey.

Background and Objectives: Tuberculosis (TB) is one of the most common infectious diseases in developing countries. The resistance of the causative agent, Mycobacterium tuberculosis, to two or more first-line anti-TB drugs results in multidrug-resistant (MDR) TB, posing a serious challenge to the control of TB worldwide. This study was designed to determine the changes in drug resistance over time in TB strains isolated from patients in all departments of Uludağ University Hospital in western Türkiye. Materials and Methods: We retrospectively analyzed 104,598 clinical samples sent to our laboratory for the investigation of the presence of TB between 1996 and 2023. BACTEC 460 TB, BACTEC MGIT 960 culture systems and Löwenstein-Jensen medium were used for the culture of these samples. The susceptibility of M. tuberculosis complex strains grown in culture to isoniazid (INH) (0.1 µg/mL), rifampicin (RIF) (1.0 µg/mL), ethambutol (ETB) (5.0 µg/mL) and streptomycin (SM) (1.0 µg/mL) antibiotics was studied according to the manufacturer's recommendation. Results: Out of 104,598 patient samples, 2752 (2.6%) were culture-positive, and the susceptibility test results of 1869 of these were analyzed. Of the isolates, 358 (19.2%) were found to be resistant to at least one first-line drug, i.e., INH, RIF, ETB, or SM. In addition, 2.9% were resistant to two or more first-line drugs. Conclusions: Drug susceptibility testing is essential to ensure the optimal treatment and control of drug-resistant TB strains. This study highlights the value of ongoing efforts to control tuberculosis drug resistance in the fight against this disease.

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57. Impact of sublineage diversity on intrinsic susceptibility of Beijing genotype Mycobacterium tuberculosis.

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Li H(#)(1), Zhang G(#)(1), Ma Z(#)(1), Guo H(2), Shang Y(1), Yao C(1), Li S(3), Pang Y(4), Pan J(5).

Author information:
(1)Department of Bacteriology and Immunology, Beijing Chest Hospital, Capital Medical University/Beijing Tuberculosis and Thoracic Tumor Research Institute, Postal No 9, Beiguan Street, Tongzhou, 101149, Beijing, People's Republic of China.
(2)Microbiological Laboratory, Shangqiu City Center for Disease Control and Prevention, Shangqiu, 476000, Henan, People's Republic of China.
(3)Department of Bacteriology and Immunology, Beijing Chest Hospital, Capital Medical University/Beijing Tuberculosis and Thoracic Tumor Research Institute, Postal No 9, Beiguan Street, Tongzhou, 101149, Beijing, People's Republic of China. lss9011@126.com.
(4)Department of Bacteriology and Immunology, Beijing Chest Hospital, Capital Medical University/Beijing Tuberculosis and Thoracic Tumor Research Institute, Postal No 9, Beiguan Street, Tongzhou, 101149, Beijing, People's Republic of China. pangyupound@163.com.
(5)Department of Bacteriology and Immunology, Beijing Chest Hospital, Capital Medical University/Beijing Tuberculosis and Thoracic Tumor Research Institute, Postal No 9, Beiguan Street, Tongzhou, 101149, Beijing, People's Republic of China. panjunhua0809@163.com.
(#)Contributed equally

Tuberculosis (TB) remains a significant global health issue, with drug-resistant TB posing a major challenge. The genetic lineage of Mycobacterium tuberculosis (Mtb) is known to influence various aspects, including drug resistance. Still, the relationship between different lineages and drug resistance levels, especially in the context of the Beijing genotype, requires further exploration. This study aimed to investigate the disparities in drug resistance among diverse lineages of Mtb. We analyzed 193 clinical isolates from drug-resistant TB patients, among them 91.2% were MDR/pre-XDR-TB. Samples were collected from patients at specific hospitals between 2014 and 2020. The isolates were

subjected to smear microscopy, sputum culture, minimum inhibitory concentration (MIC) testing, and whole-genome sequencing (WGS). The MIC distributions and resistance levels of drugs like INH, AMK, RIF, EMB, and FQ were analyzed, and the association between lineages and drug resistance was determined using statistical tests. Our results showed significant differences in the MIC distributions and resistance levels of INH and AMK between lineages 2.2 and 2.3. Lineage 2.3.2 was a protective factor for high-level INH resistance, and lineage 2.3 was a protective factor for high-level AMK resistance. The L2.3.6 strain had a high proportion of high-level resistance to INH and AMK. This study provides evidence for the evolution and spread of the modern Beijing genotype of Mtb. It suggests that L2.3.6 will have the potential to become the main sublineage of tuberculosis for the spread of drug-resistant tuberculosis and the necessity of pedigree testing of drug-resistant strains in clinical treatment.

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58. DRTB-HDT: a randomized controlled trial of two adjunctive host-directed therapies in rifampin-resistant tuberculosis.

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Tukvadze N(1)(2), Mashatole S(3), Jacobs A(4)(5), Ngwanto T(3), Heinrich N(6), Van Rie A(7), Crudu V(8), Tudor E(8), Goginashvili L(9), Ibraim E(10), Khosa C(11), Howell P(12), Rajaram S(12), Naidoo K(12), Niemann S(13)(14), Reither K(4)(5), Wallis RS(3)(15).

Author information:
(1)Swiss Tropical and Public Health Institute, Kreuzstrasse 2, 4123, Allschwil, Switzerland. nestani.tukvadze@swisstph.ch.
(2)University of Basel, Petersplatz 1, 4001, Basel, Switzerland. nestani.tukvadze@swisstph.ch.
(3)The Aurum Institute NPC, 29 Queens Road, Parktown, 2193, Johannesburg, South

Africa.
(4)Swiss Tropical and Public Health Institute, Kreuzstrasse 2, 4123, Allschwil, Switzerland.
(5)University of Basel, Petersplatz 1, 4001, Basel, Switzerland.
(6)Ludwig-Maximilians-Universitaet, Geschwister-Scholl-Platz 1, 80539, Munich, Germany.
(7)University of Antwerp, Prinsstraat 13, 2000, Antwerp, Belgium.
(8)Institutia Medico Sanitara Publica - Institutul de Pneumologie, "Chiril Draganuic" 13 Virnav Street, Chisinau, MD-2025, Moldova.
(9)National Center for Tuberculosis and Lung Diseases, 8 Adjara Street, 0101, Tbilisi, Georgia.
(10)Institutul de Pneumoftiziologie Marius Nasta, Sos. Viilor Nr. 90 Sector 5 CP, Bucharest, Romania.
(11)Instituto Nacional de Saúde, EN1, Barrio da Vila - Parcela N. 3943, Distrito de Marracuene Provinicia de Maputo, Maputo, Mozambique.
(12)WITS Health Consortium, 31 Princess of Wales Terrace, Parktown, 2193, Johannesburg, South Africa.
(13)Forschungszentrum Borstel Leibniz Lungenzentrum, Parkallee 1-40, 23845, Borstel, Germany.
(14)German Center for Infection Research (DZIF), Parkallee 1-40, 23845, Borstel, Germany.
(15)Case Western Reserve University School of Medicine, 9501 Euclid Ave., Cleveland, OH, 44106, USA.

BACKGROUND: Tuberculosis (TB) is a leading cause of morbidity and mortality worldwide. Current TB treatments are inadequate, requiring participants closely adhere to multi-drug regimens that are long, complex, and often poorly tolerated. In addition to these well-recognized shortcomings, current TB treatments, particularly those for rifampicin-resistant tuberculosis, leave a majority of cured participants with permanent, clinically significant lung impairment and radiographic evidence of bronchiectasis and fibrosis. This project will determine if two adjunctive host-directed therapies (HDTs) can prevent these poor outcomes.
METHODS: Three hundred thirty participants with RIF-R TB and baseline risk factors for poor outcome will be enrolled in a randomized, controlled, 3-armed multi-centre trial, with clinical sites in Romania, Moldova, Georgia, Mozambique, and South Africa. All participants will receive standard multidrug therapy according to national guidelines. Those participants randomized to the experimental arms will in addition receive either CC-11050 (dovramilast) or metformin. Co-primary efficacy endpoints will examine effects on lung function (measured by spirometry) and infection (measured as time to stable sputum culture conversion). A sub-study will examine quantitative change in lung radiodensity by CT scan.
DISCUSSION: These selected host-directed therapies candidates represent two

complementary strategies: reducing inflammation vs inducing host cell anti-microbial activity, respectively. Both candidates are supported by data from preclinical and clinical studies. If successful, this ground-breaking project will increase Europe's capacity to control drug resistant tuberculosis by developing new treatments that increase the likelihood of cure and reduce the risk of life-long disability.
TRIAL REGISTRATION: EudraCT Number: 2020-004295-18. South African National Clinical Trial Registration (SANCTR) Number: DOH-27-042021-8345.

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59. Evaluating the immunogenicity and safety of ID93 + GLA-SE in BCG-vaccinated healthy adults: a systematic review and meta-analysis of randomized controlled Trials.

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Siddiqui E(1), Khan MS(1), Khalid M(1), Chandani HK(1), Naeem U(1), Khan MM(2), Wasti SO(3).

Author information:
(1)Jinnah Sindh Medical University, Karachi, Pakistan.
(2)Jinnah Sindh Medical University, House No. 9 Sheet 4 Shah Wali Ullah, Nagar Orange, Karachi 75510, Pakistan.
(3)Independent Author.

BACKGROUND: Tuberculosis (TB), caused by Mycobacterium tuberculosis (Mtb), is an ancient disease that continues to pose a significant threat to global public health. Although the BCG vaccine, developed in the 1920s, remains the only approved TB vaccine, it has limited efficacy, particularly against pulmonary TB in adults. The ID93/GLA-SE vaccine, a recombinant subunit vaccine, shows promise

by triggering immune solid responses and could be a key solution in combating TB, particularly in the face of rising drug-resistant strains and suboptimal current vaccines. It has the potential to address the unmet need for more effective interventions against drug-resistant TB, a growing global health issue that continues to challenge existing treatment options.
OBJECTIVE: To evaluate the immunogenicity and safety of ID93 + GLA-SE in BCG-vaccinated healthy adults.
METHODS: A comprehensive electronic search on PubMed (Medline), ScienceDirect, EMBASE, Scopus, and Cochrane Central database was conducted from inception till August 2024 for randomized controlled trials (RCTs) with a target population of BCG-vaccinated healthy adults. This review was conducted according to (PRISMA) criteria and registered with PROSPERO (CRD42024601450). This meta-analysis used Review Manager and forest plots for visual display. The outcomes were displayed as risk ratios (RR) with a 95% confidence interval.
RESULTS: The ID93 + GLA-SE vaccine showed strong immunogenicity, particularly in high doses, with robust IgG responses sustained up to day 421 in all studies, significantly higher than baseline, and seroconversion rates remained high through day 84. CD4 T-cell responses peaked after the third dose and remained elevated through day 421, whereas CD8 T-cell responses were minimal. Regarding adverse effects, the ID93 + GLA-SE vaccine significantly increases fatigue (RR 3.24, $p = 0.005$), myalgia (RR 5.82, $p < 0.0001$), and injection site pain (RR 4.12, $p < 0.00001$), compared to placebo, with consistent results across both high and low doses. However, there were no significant differences for upper respiratory tract infections, 0.83 (95% CI 0.38-1.84, $p = 0.87$) or 1.77 (95% CI 0.77-4.10, $p = 0.18$) headaches. Dose optimization remains crucial due to the higher side effect risks of increased doses.
CONCLUSION: The ID93 + GLA-SE vaccine shows a solid safety profile and enhances immune responses, especially IgG and CD4+ T-cell activity, which is crucial for TB defense. Higher doses improve efficacy but increase side effects, highlighting the need for dose optimization. As a potential alternative to the BCG vaccine, especially in drug-resistant TB regions, further research should refine dosage and assess long-term safety.

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60. The prevalence of undernutrition and associated risk factors in people with tuberculosis in Lao People's Democratic Republic.

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Inthavong D(1), Elsayed H(2), Keonakhone P(3), Seevisay V(4), Souksanh S(4), Suthepmany S(1), Chanthavong M(1), Keodavong X(1), Kommanivanh P(1), Siphanthong P(1), Sengmany P(3), Sisounon B(3), Sebert J(4), Yanagawa M(2), Morishita F(2), Nishikiori N(5), Yamanaka T(5).

Author information:
(1)National Tuberculosis Control Centre, Vientiane, Lao People's Democratic Republic.
(2)Integrated Communicable Disease Control, World Health Organization Regional Office for the Western Pacific, Manila, Philippines.
(3)National Nutrition Centre, Vientiane, Lao People's Democratic Republic.
(4)World Health Organization Representative Office for Lao PDR, Vientiane, Lao People's Democratic Republic.
(5)Global Tuberculosis Programme, World Health Organization, Geneva, Switzerland.

OBJECTIVE: Undernutrition is common in individuals with tuberculosis (TB). There is a bidirectional association between having TB and undernutrition; undernutrition increases the risk of having active TB, and having TB worsen undernutrition by reducing appetite and food intake. Despite World Health Organization (WHO) recommendations for comprehensive nutritional assessment and counselling for people with TB, systematic implementation is lacking in Lao People's Democratic Republic (Lao PDR), leading to an insufficient understanding of undernutrition prevalence in this population.
METHODS: A facility-based cross-sectional survey was conducted between March 2022 and March 2023 in six central and provincial hospitals in Lao PDR. We assessed the prevalence of undernutrition in 312 people diagnosed with TB at TB diagnosis using body mass index (BMI). Undernutrition was defined as a BMI < 18.5 kg/m2, and severe undernutrition as a BMI below 16.5 kg/m2. Data on demographic, clinical and economic information and nutritional status were extracted from an intervention study assessing the effect of nutritional counselling and feeding on the financial burden of TB and TB treatment outcomes.
RESULTS: Of 312 participants, 40.7% (n = 127) were with undernutrition (BMI < 18.5 kg/m2) at the time of TB diagnosis. 20.5% (n = 64) with severe undernutrition (BMI < 16.5 kg/m2). Factors significantly associated with undernutrition included age group 15-24 years (Adjusted odds ratio (AOR) 6.9, 95% confidence interval [95%CI]: 2.2-23.2), drug-resistant TB (AOR 3.2, 95%CI: 1.0-11.8), experiences of hospitalization until TB diagnosis (AOR 3.4, 95%CI:

2.0-5.9), self-reported weight loss (AOR 7.8, 95%CI: 2.3-36.4), and below the poverty line at TB diagnosis (AOR 1.9, 95%CI: 1.0-3.6).
CONCLUSION: A high prevalence of undernutrition was observed in people diagnosed with TB at their diagnosis in Lao PDR. The findings underscore the urgent need for systematic nutritional assessment and counselling as integral components of TB care to identify and address undernutrition, thereby enhancing overall health outcomes for individuals with TB.

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PMID: 40540510 [Indexed for MEDLINE]

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

61. Retrospective epidemiological analysis of pulmonary tuberculosis in the older adult and characterization of rifampicin resistance-associated rpoB mutations in Nantong City, China (2014-2023).

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Zhu H(#)(1), Wang S(#)(1), Zhao X(2), Wu P(3), Chen J(4), Li F(1).

Author information:
(1)Department of Clinical Laboratory, Affiliated Nantong Hospital of Shanghai University (The Sixth People's Hospital of Nantong), Nantong, China.
(2)Department of Public Health, Affiliated Nantong Hospital of Shanghai University (The Sixth People's Hospital of Nantong), Nantong, China.
(3)Qinzao Health Service Center of Nantong, Nantong, China.
(4)Department of Chronic Infectious Diseases, Nantong Center for Disease Control and Prevention, Nantong, China.
(#)Contributed equally

OBJECTIVE: To analyze the prevalence trend of older adult pulmonary tuberculosis

(ETB) and the distribution and outcome of rifampicin-resistant rpoB gene mutation in ETB patients in Nantong.
METHODS: The pulmonary tuberculosis patients' data in Nantong from 2014 to 2023 were from Tuberculosis Information Management Syste and ETB and rifampicin-resistant rpoB mutation patients were retrospectively analyzed.
RESULTS: From 2014 to 2023, the overall standardized incidence of ETB in Nantong showed a trend of rapid decline and tended to a stable trend stabilized. A total of 140 older adult patients with rifampin resistance, aged 60-69 years, 87 cases (62.1%). single-gene mutation Probe E mutations were the most frequent, observed in 39 cases (60.0%). Specifically, 52 cases (80.00%) were resistant to rifampicin, and Probe E of 31 cases (59.62%) showed the most mutations. The outcome of ETB patients with rifampicin resistance were significantly correlated with treatment classification, rifampicin resistance, Xpert MTB first test, and 0-month sequential sputum positivity.
CONCLUSION: The number of ETB in Nantong from 2014 to 2023 showed a rapid decline and stabilized. The rpoB mutations in the ETB rifampicin-resistant patients were mainly single-gene mutations. The authorities should formulate effective regional prevention and control measures based on the characteristics of the ETB rifampicin-resistant patients.

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62. Heat-inactivated Mycobacterium bovis and P22PI protein immunocomplex: Two candidates for use as immunostimulants of innate immune response.

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Agulló-Ros I(1), Burucúa MM(2), Cheuquepán FA(3), Domínguez M(4), Sevilla IA(5), Martínez R(6), Plá N(7), Risalde MA(8), Marin MS(3).

Author information:
(1)Departamento de Anatomía y Anatomía Patológica Comparadas y Toxicología, Grupo de Investigación en Sanidad Animal y Zoonosis (GISAZ), UIC Zoonosis y Enfermedades Emergentes ENZOEM, Universidad de Córdoba, Córdoba, Spain.

(2)Departamento de Biología, Facultad de Ciencias Exactas y Naturales, Universidad Nacional de Mar del Plata, Mar del Plata, Buenos Aires, Argentina.
(3)Departamento de Biología, Facultad de Ciencias Exactas y Naturales, Universidad Nacional de Mar del Plata, Mar del Plata, Buenos Aires, Argentina; Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Buenos Aires, Argentina.
(4)Servicio de Inmunología Microbiana, Centro Nacional de Microbiología, Instituto de Salud Carlos III, Majadahonda, Madrid, Spain.
(5)Animal Health Department, NEIKER-Instituto Vasco de Investigación y Desarrollo Agrario, Derio, Bizkaia, Spain.
(6)Departamento de Sanidad Animal, Grupo de Investigación en Sanidad Animal y Zoonosis (GISAZ), UIC Zoonosis y Enfermedades Emergentes ENZOEM, Universidad de Córdoba, Córdoba, Spain.
(7)Facultad de Ciencias Agrarias, Universidad Nacional de Mar del Plata, Mar del Plata, Buenos Aires, Argentina.
(8)Departamento de Anatomía y Anatomía Patológica Comparadas y Toxicología, Grupo de Investigación en Sanidad Animal y Zoonosis (GISAZ), UIC Zoonosis y Enfermedades Emergentes ENZOEM, Universidad de Córdoba, Córdoba, Spain; CIBERINFEC, ISCIII - CIBER de Enfermedades Infecciosas, Instituto de Salud Carlos III, Madrid, Spain. Electronic address: v12rimom@uco.es.

Tuberculosis (TB), caused by members of the Mycobacterium tuberculosis complex, remains a critical global health challenge, affecting humans and a wide range of domestic and wild animals. Despite the availability of anti-TB drugs, cure rates remain suboptimal, exacerbated by the rise of multidrug-resistant TB strains. The Bacille Calmette-Guérin (BCG) vaccine, the only licensed vaccine against TB, has demonstrated efficacy in reducing lesion severity and bacterial burden in animals, as well as lowering TB-related and all-cause mortality in infants. However, BCG presents several safety concerns inherent to live vaccines. To overcome these limitations, exploring alternative vaccine candidates that do not incorporate live mycobacteria is crucial. This study aimed to evaluate and compare the immunostimulatory potential of two candidates based in mycobacteria inactivated or their derivatives, heat-inactivated Mycobacterium bovis (HIMB) and P22PI protein immunocomplex (P22PI), in bovine foetal lung cells. To assess the expression of innate immune components, including Toll-like receptors (TLRs), cathelicidins, and cytokines, bovine foetal lung were exposed to different concentrations of HIMB and P22PI immunostimulants, starting at 7.8×10^6 CFU/ml and 10 µg/ml, respectively. These initial concentrations were subsequently diluted to 1/2 and 1/10 to evaluate dose-dependent effects. Our findings reveal that both HIMB and P22PI significantly stimulate innate immune mechanisms, as evidenced by the upregulation of TLR2 and TLR4, alongside the induction of BMAP28 cathelicidin, tumour necrosis factor alpha (TNFA) and interferons (IFNs). These results suggest their potential to orchestrate a robust innate immune response providing valuable insights into the immunological

mechanisms underlying the protective effects of these immunostimulants. This underscores their potential role in in vivo studies as vaccine candidates. Furthermore, their ability to enhance antigen recognition via TLR and induce pro-inflammatory cytokines also indicates broader applications in immune modulation, potentially extending protection against heterologous pathogens through trained immunity.

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63. An exploratory study on the application of nanopore sequencing for detecting Mycobacterium tuberculosis drug resistance in respiratory specimens.

BMC Pulm Med. 2025 Jun 3;25(1):279. doi: 10.1186/s12890-025-03747-1.

Wei N(#)(1)(2), Du F(#)(1)(2), Nie W(#)(3), Nong Y(4), Lin Y(1), Huang A(1), Xi S(5), Lan Y(2), Luo X(2), Yang S(6), Zhu Q(7).

Author information:
(1)Department of Tuberculosis, The Fourth People's Hospital of Nanning, NO.1 Changgang-two-li Road, Nanning, Guangxi, 530023, China.
(2)Guangxi Medical University, Nanning, China.
(3)Department of Tuberculosis, Beijing Chest Hospital, Capital Medical University, Beijing, China.
(4)Department of Medical, The Fourth People's Hospital of Nanning, Nanning, China.
(5)Department of Clinical Laboratory, The Fourth People's Hospital of Nanning, Nanning, China.
(6)Administrative Office, The Fourth People's Hospital of Nanning, NO.1 Changgang-two-li Road, Nanning, Guangxi, 530023, China. 13407719256@163.com.
(7)Department of Tuberculosis, The Fourth People's Hospital of Nanning, NO.1 Changgang-two-li Road, Nanning, Guangxi, 530023, China. zhuqingdong2003@126.com.
(#)Contributed equally

BACKGROUND: This study aimed to evaluate the diagnostic efficacy of nanopore sequencing for Mycobacterium tuberculosis (MTB) drug resistance in respiratory

specimens from pulmonary tuberculosis (PTB) patients. It compared it to the Xpert MTB/RIF and fluorescent polymerase chain reaction (PCR) melting curve to explore the validity and feasibility of detecting MTB drug resistance in respiratory specimens.
METHODS: This study retrospectively analyzed 52 respiratory specimens. The proportional method applied the phenotypic drug susceptibility test (pDST) to respiratory specimens. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), consistency statistic (kappa) with phenotypic drug susceptibility testing (pDST), and the area under the curve (AUC) from the receiver operating characteristic (ROC) curve were calculated for nanopore sequencing, Xpert MTB/RIF, and fluorescent PCR melting curve. These calculations used the pDST results as the reference standard.
RESULTS: Among the resistance mutation genes detected by nanopore sequencing, rpoB, and katG were the most frequent, followed by embB, rpsL, gyrA, inhA, ahpC, gyrB, gid, and rrs. In bronchoalveolar lavage fluid (BALF) specimens, nanopore sequencing showed high sensitivity (100.00%,90.32%,82.35%,82.35%,100.00%,76.92%), specificity (70.00%,81.82%,88.00%,96.00%93.75%,93.10%0.100.00%), and AUC values (0.85,0.86,0.85, 0.89,0.97,0.85) for rifampicin (RIF), isoniazid (INH), ethambutol (EMB), streptomycin (SM), levofloxacin (LFX), moxifloxacin (MFX). Nanopore sequencing exhibited good detection efficacy (kappa value ≥ 0.70) and perfect diagnostic resistance value (AUC value ≥ 0.85). For RIF, nanopore sequencing showed Kappa values of 0.01 and 0.38 and AUC values of 0.02 and 0.18 higher than the Xpert MTB/RIF and fluorescent PCR melting curve, respectively; for INH, nanopore sequencing had a higher Kappa value of 0.65 and a higher AUC value of 0.32 than the fluorescent PCR melting curve. Nanopore sequencing provided superior overall performance.
CONCLUSION: Nanopore sequencing has significant technical advantages and clinical application potential in detecting MTB drug resistance. Its rapid and highly accurate detection capabilities support early diagnosis and personalized treatment of drug-resistant MTB. As the technology continues to mature and the cost is further reduced, it is expected that nanopore sequencing technology will play a more important role in MTB resistance detection.

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PMID: 40462071 [Indexed for MEDLINE]

Conflict of interest statement: Declarations. Ethics approval and consent to participate: The protocol was approved on February10, 2023, by the Human Research Ethics Committee of the Fourth People’s Hospital of Nanning City, Guangxi Zhuang Autonomous Region (opinion number [2023]24). All research

participants or their legal guardians have obtained informed consent. All methods were carried out in accordance with relevant guidelines and regulations that is Declaration of Helsinki. Consent for publication: Not applicable. Competing interests: The authors declare no competing interests.

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

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

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

Tuberculosis is one of the diseases causing high rates of morbidity and mortality in several countries. However, efforts in the use of diagnostic methods for tuberculosis and the detection of drug resistance are essential to reduce cases. Since 2015, rapid molecular diagnostic tests have been implemented in Panama, enabling the detection of drug resistance, mainly rifampicin and isoniazid, in patients with suspected tuberculosis. This study aimed to identify mutations in Mycobacterium tuberculosis complex strains with resistance to rifampicin and isoniazid using GenoType MTBDRplus. It is a retrospective study reviewing the results of the GenoType MTBDRplus version 2.0 test from 2015 to 2021. Strains not identified as Mycobacterium tuberculosis complex and those that did not show a mutation pattern and were categorized as sensitive were excluded. Data analysis was carried out using the Chi-square tests, Pearson's Correlation, and principal components analysis. A total of 4,301 strains were analyzed, of which 8.8% were detected with mutation or resistance probes in one or more of the genes analyzed: 56.0% in the rpoβ gene, 11.9% in the inhA gene, and 8.2% in the katG gene. In addition, other mutations such as rpoβ/inhA and rpoβ/katG were detected in 9.5% and 13.5% of cases, respectively. Thirty-eight resistance patterns were identified, with H526D and S531L being the most frequent mutations in the rpoB gene, and S315T1 and C-15T are the most common in katG and inhA, respectively. The resistance patterns detected by the GenoType MTBDRplus assay highlight the genetic variability of drug resistance in the country and emphasize the need to implement epidemiological surveillance methodologies. Integrating patient clinical data with genetic variation information is essential for improving disease control and understanding

transmission dynamics and drug resistance acquisition. These findings also provide important insights for guiding tuberculosis treatment strategies in Panama, supporting the use of molecular tools for the early detection of drug resistance, enhancing our understanding of the epidemiology, and informing clinical decision-making.
IMPORTANCE: This study focuses on understanding how Mycobacterium tuberculosis strains in Panama develop resistance. With tuberculosis (TB) cases becoming harder to treat due to drug resistance, especially after the disruptions caused by the COVID-19 pandemic, rapid and accurate diagnosis is crucial. By using advanced molecular tests to identify specific genetic mutations in drug-resistant TB strains, this research helps improve treatment decisions, leading to better outcomes for patients. Understanding these mutations also aids in controlling the spread of TB. Given the rising global concern over drug-resistant TB, the findings of this study are important not only for Panama but also for other regions facing similar challenges.

DOI: 10.1128/spectrum.02400-24
PMID: 40488462

65. An improved catalogue for whole-genome sequencing prediction of bedaquiline resistance in Mycobacterium tuberculosis using a reproducible algorithmic approach.

Microb Genom. 2025 Jun;11(6):001429. doi: 10.1099/mgen.0.001429.

Adlard D(1), Joseph L(2), Webster H(1), O'Reilly A(1), Knaggs J(1), Peto TEA(1)(3)(4), Crook DW(1)(3)(4), Omar SV(2), Fowler PW(1)(3)(4).

Author information:
(1)Nuffield Department of Medicine, John Radcliffe Hospital, University of Oxford, Headley Way, Oxford, UK.
(2)Centre for Tuberculosis, National Institute for Communicable Diseases a Division of the National Health Laboratory Service, Johannesburg, South Africa.
(3)Health Protection Research Unit in Healthcare Associated Infections and Antimicrobial Resistance, University of Oxford, Oxford, UK.
(4)National Institute of Health Research Oxford Biomedical Research Centre, John Radcliffe Hospital, Headley Way, Oxford, UK.

Bedaquiline (BDQ) has only been approved for use for just over a decade and is a key drug for treating multidrug-resistant tuberculosis; however, rising levels of resistance threaten to reduce its effectiveness. Catalogues of mutations associated with resistance to BDQ are key to detecting resistance genetically for either diagnosis or surveillance. At present, building catalogues requires

considerable expert knowledge, often requires the use of complex grading rules and is an irreproducible process. We developed an automated method, catomatic, that associates genetic variants with resistance (or susceptibility) using a two-tailed binomial test with a stated background rate and applied it to a dataset of 11,867 Mycobacterium tuberculosis samples with whole-genome and BDQ susceptibility testing data. Using this framework, we investigated how to best classify variants and the phenotypic significance of minor alleles. The genes mmpS5 and mmpL5 are not directly associated with BDQ resistance, and our catalogue of Rv0678, atpE and pepQ variants attains a cross-validated sensitivity and specificity of 79.4±1.8% and 98.5±0.3%, respectively, for 94±0.4% of samples. Identifying samples with subpopulations containing Rv0678 variants improves sensitivity, and detection thresholds in bioinformatic pipelines should therefore be lowered. By using a more permissive and deterministic algorithm trained on a sufficient number of resistant samples, we have reproducibly constructed a catalogue of BDQ resistance-associated variants that is comprehensive and accurate.

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66.Differences found in patient characteristics of migrant tuberculosis sub-populations within low TB incidence European countries, 2014-2020.

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Jackson S(1), Hauer B(2), Guthmann JP(3), O Meara M(4), Sizaire V(5), Nordstrand K(6), Koch A(7)(8), Häcker B(9), de Vries G(10), Jonsson J(11), Kristensen KL(7)(12), de Oñate WA(13), Soini H(14), Domaszewska T(2).

Author information:
(1)Health Protection Surveillance Centre, Health Service Executive, Dublin, Ireland. jacksos2@tcd.ie.
(2)Department of Infectious Disease Epidemiology, Robert Koch Institute, Berlin, Germany.
(3)Santé Publique France, Saint-Maurice, Paris, France.
(4)Health Service Executive, National Health Protection Office, Dublin, Ireland.
(5)FARES, Brussels, Belgium.
(6)Norwegian Institute of Public Health, Oslo, Norway.
(7)Statens Serum Institut, Copenhagen, Denmark.

(8)Rigshospitalet University Hospital, Copenhagen, Denmark.
(9)German Central Committee Against Tuberculosis (DZK), Berlin, Germany.
(10)National Institute for Public Health and the Environment (RIVM), Bilthoven, Netherlands.
(11)Folkhälsomyndigheten/Public Health Agency of Sweden, Stockholm, Sweden. jerker.jonsson@folkhalsomyndigheten.se.
(12)Department of Pulmonary and Infectious Diseases, Nordsjaellands Hospital, Hilleroed, Denmark.
(13)BELTA - Belgian Lung and Tuberculosis Association, Brussels, Belgium.
(14)Finnish Institute for Health and Welfare, Helsinki, Finland.

INTRODUCTION: In low TB incidence countries, prevention and care activities addressing migrant populations are essential for TB control. Understanding characteristics of TB patients in the migrant population is important for planning and providing appropriate care. This study aims to inform prevention and care strategies by describing characteristics of TB patients within migrant subpopulations in Europe to understand whether differences exist in their patient profiles.
METHODS: This cross-sectional descriptive study of migrants with TB reported to the European Surveillance System (2014-2020) from 23 low incidence European countries describes characteristics of different subgroups, according to TB epidemiological indicators and interval between arrival and notification.
RESULTS: Migrants with TB originating from very high TB incidence countries had the highest proportion of people living with HIV (7%) and highest extrapulmonary TB proportion (44%). Patients from high incidence countries had the highest proportion with previous TB diagnosis (14%), first line (12%) and multidrug (6%) resistances. Compared to all patients, patients arriving from the 10 countries with the highest crude incidence rates were on average 9 years younger (median age 25 vs 34) and more often male (M:F ratio 2.6 vs. 1.8). Patients notified < 2 years after arrival had higher proportions diagnosed with PTB (67%) and MDR-TB (4%), as well as people living with HIV (7%).
DISCUSSION: Unique patterns in patient characteristics were observed which varied by origin and destination. Improving European TB preparedness within the context of migration requires timely and complete international data alongside continuous access to quality TB care, not only at entry, and expanded opportunities for diagnosis given levels of extrapulmonary TB observed.

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PMID: 40457198 [Indexed for MEDLINE]

Conflict of interest statement: Declarations. Ethics approval and consent to

participate: As this was a secondary data analysis of anonymized data with no patient interaction or interventions, this did not meet the criteria of research using personally identifiable data which requires approval by a research ethics committee under the Helsinki Declaration [16]. All data processing was compliant with the General Data Protection Regulations [17]. Consent for publication: Not applicable. Competing interests: The authors declare no competing interests.

67. The global economic burden of antibiotic-resistant infections and the potential impact of bacterial vaccines: a modelling study.

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Naylor NR(1)(2), Hasso-Agopsowicz M(3), Kim C(4), Ma Y(5), Frost I(3), Abbas K(4)(6)(7)(8), Aguilar G(9), Fuller N(4), Robotham JV(2), Jit M(4).

Author information:
(1)Department of Health Services Research and Policy, The London School of Hygiene and Tropical Medicine, London, UK nichola.r.naylor@gmail.com.
(2)HCAI, Fungal, AMR, AMU & Sepsis Division, UK Health Security Agency, London, UK.
(3)Immunization, Vaccines & Biologicals, World Health Organization, Geneva, Switzerland.
(4)Department of Infectious Disease Epidemiology, London School of Hygiene & Tropical Medicine, London, UK.
(5)Aquarius Population Health Ltd, London, UK.
(6)School of Tropical Medicine and Global Health, Nagasaki University, Nagasaki, Japan.
(7)Institute of Tropical Medicine, Nagasaki University, Nagasaki, Japan.
(8)Public Health Foundation of India, New Delhi, India.
(9)University of Oxford, Oxford, UK.

INTRODUCTION: Antibiotic resistance (ABR) may increase hospital costs, utility loss and mortality risk per patient. Understanding these losses at national, regional and global scales is necessary for efficiently tackling ABR. Our aim is to estimate the global economic burden of antibiotic-resistant infections and the potential for bacterial vaccines to mitigate this burden.
METHODS: We take healthcare system and labour productivity perspectives. Hospital cost-per-case and length-of-stay estimates were calculated through meta-analyses and reviewing published systematic reviews. Unit labour productivity losses were estimated through a human capital approach. Modelled estimates were used where secondary data were missing. Death and incidence data were combined with unit cost data to estimate the economic burden associated with ABR in 2019, and the potential costs averted (in 2019 US$) based on uptake

scenarios of vaccines that currently exist or are likely to be developed.
RESULTS: Multidrug-resistant tuberculosis had the highest mean hospital cost attributable to ABR per patient, the range was US$3000 in lower-income settings to US$41 000 in high-income settings, with carbapenem-resistant infections associated with a high cost-per-case of US$3000-US$7000 depending on syndrome. ABR was associated with a median value of US$693 billion (IQR: US$627 bn-US$768 bn) in hospital costs globally, with US$207 bn (IQR: US$186 bn-US$229 bn) potentially avertable by vaccines. Productivity losses were quantified at almost US$194 billion, with US$76 bn avertable by vaccines.
CONCLUSIONS: The economic burden of ABR is associated with high levels of hospital bed-days occupied, hospital spending and labour productivity losses globally and should, therefore, remain high on national and international policy agendas. Vaccines against Staphylococcus aureus, Escherichia coli and Klebsiella pneumoniae would avert a substantial portion of the economic burden associated with ABR. More robust evidence, particularly in low-income countries, on the hospital costs, associated with and attributable to ABR, is needed.

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Conflict of interest statement: Competing interests: None declared.

68.Risk factors on length of stay among pulmonary tuberculosis patients: A systematic review and meta-analysis.

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Weiangkham D(1), Umnuaypornlert A(2)(3), Saokaew S(2)(3)(4), Wongcharoen N(1), Prommongkol S(5), Ponmark J(1).

Author information:
(1)School of Nursing, University of Phayao, Phayao, 56000 Thailand.
(2)Division of Social and Administrative Pharmacy (SAP), Department of Pharmaceutical Care, School of Pharmaceutical Sciences, University of Phayao, Phayao, 56000, Thailand.
(3)Unit of Excellence on Clinical Outcomes Research and IntegratioN (UNICORN), School of Pharmaceutical Sciences, University of Phayao, Phayao, 56000, Thailand.
(4)Center of Excellence in Bioactive Resources for Innovative Clinical

Applications, Chulalongkorn University, Bangkok, 10330, Thailand.
(5)Mahidol Bangkok School of Tropical Medicine (Mahidol-BSTM), Faculty of Tropical Medicine, Mahidol University, Bangkok, 10400 Thailand.

BACKGROUND: Pulmonary Tuberculosis (PTB) remains a pressing public health concern. Long hospital stays for PTB patients can overburden both patients and healthcare systems.
OBJECTIVE: To identify the key factors contributing to extended length of stay in PTB patients.
INFORMATION SOURCES: Four electronic databases (PubMed, Scopus, Embase, and CINAHL) were systematically searched from inception to January 1, 2023.
METHODS: The articles were screened and performed according to Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA). Inclusion criteria were PTB patients diagnosed by doctors and studies reporting factors affecting length of stay. Exclusion criteria were review articles, case study, conferences abstract, and proceedings. Study quality was assessed using the Newcastle-Ottawa Scale (NOS). A random-effects model was used to analyzed risk factors for length of stay. Heterogeneity was employed using I2 and Q statistics. Forest plots displayed effect sizes (ES) and 95 % confidence intervals. STATA 14.2 was used for meta-analysis.
RESULTS: A total of 1,190 studies were screened from reputable electronic databases, six studies comprised of 9,231 participants were included. Meta-analysis revealed that they are six risk factors associated with longer length of stay including; older age (OR 1.50, 95 % CI 1.07-2.09, p = 0.019), comorbidity (OR 1.44, 95 % CI 1.17-1.78, p = 0.001), HIV patient (OR 1.40, 95 % CI 1.16-1.69, p = 0.001), patients with ADR (OR 2.19, 95 % CI 1.47-3.26, p < 0.001), MDR TB (OR 3.16, 95 % CI 2.31-4.32, p < 0.001), and miliary TB (OR 1.37, 95 % CI 1.10-1.70, p = 0.004) with minimal heterogeneity [(I2 = 34.2 %, p = 0.207), (I2 = 43.1 %, p = 0.118), (I2 = 0.0 %, p = 0.573), (I2 = 0.0 %, p = 0.723), (I2 = 0.0 %, p = 0.366), and (I2 = 0.0 %, p = 0.753), respectively]. There was no evidence of publication bias according to Begg's and Egger's test.
CONCLUSIONS: In conclusion, six risk factors were identified as significantly associated with longer hospital stays in PTB patients: older age, comorbidities, HIV infection, ADR, MDR-TB, and miliary TB. These findings highlight the importance of targeted interventions for these high-risk groups to reduce length of stay and alleviate the burden on healthcare systems. The results are based on a meta-analysis of six studies with minimal heterogeneity, and no evidence of publication bias was found. Future research should focus on exploring additional factors influencing length of stay, particularly in diverse populations, and evaluating the effectiveness of interventions to shorten hospital stays. Additionally, studies examining the impact of healthcare infrastructure and resource allocation on length of stay could provide valuable insights for improving patient outcomes.
REGISTRATION: This study was registered with PROSPERO, CRD4203390615.

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PMID: 40535787

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

69. Whole-Genome Sequence-Based Diversity of Mycobacterium tuberculosis Strains Isolated from a Central Western Region of Mexico.

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Negrete-Paz AM(1), Vázquez-Marrufo G(2), Rodríguez-Carlos A(3), Rivas-Santiago B(3), Vázquez-Garcidueñas MS(1).

Author information:
(1)División de Estudios de Posgrado, Facultad de Ciencias Médicas y Biológicas "Dr. Ignacio Chávez", Universidad Michoacana de San Nicolás de Hidalgo, Morelia C.P. 58020, Michoacán, Mexico.
(2)Centro Multidisciplinario de Estudios en Biotecnología, Facultad de Medicina Veterinaria y Zootecnia, Universidad Michoacana de San Nicolás de Hidalgo, Tarímbaro C.P. 58893, Michoacán, Mexico.
(3)Unidad de Investigación Biomédica de Zacatecas, Instituto Mexicano del Seguro Social-IMSS, Zacatecas C.P. 98000, Zacatecas, Mexico.

Tuberculosis remains a significant health issue in Mexico, which has one of the highest incidence rates in the Americas. This study aimed to analyze the circulating sublineages, spoligotypes, drug resistance, and transmission patterns of Mycobacterium tuberculosis in Mexico's Central Western region using whole-genome sequencing. Seventy-seven Mycobacterium tuberculosis strains underwent phenotypic drug susceptibility testing via MGIT. Genotypic resistance was assessed with TB-Profiler and Mykrobe, while phylogenetic relationships were reconstructed using Snippy and RaxML. SpoTyping identified circulating SITs and families, with a 5-SNP threshold defining genomic transmission clusters. The predominant sublineages were 4.1.1.3 (X-type, n = 19) and 4.1.2.1 (LAM, n = 11), with rare sublineages (EAI5, EAI2-Manila, and Beijing) also observed. Resistance to at least one first-line drug was found in 63.3% of strains, with streptomycin mono-resistance (24.5%) being notable. Multidrug-resistant TB was identified in 16.3% (n = 8) of strains. Five genomic clusters, involving 18.7% of strains,

were identified. This study highlights the sublineage diversity in Mexico, emphasizing its importance in global databases and resistance research. The findings, such as SIT47 in GC1, underscore the value of localized genomic studies for effective TB control.

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70. The ahpC c-54t compensatory mutation is not always a valid surrogate for isoniazid resistance in Mycobacterium tuberculosis.

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Szél V(#)(1), Phelan JE(#)(2), Georghiou SB(3), Dolinger DL(4), Clark TG(2), Niemann S(5)(6), Lőrinczi LK(1), Köser CU(7).

Author information:
(1)National Reference Laboratory for Mycobacteriology, National Koranyi Institute of Pulmonology, Budapest, Hungary.
(2)Faculty of Infectious and Tropical Diseases, London School of Hygiene & Tropical Medicine, London, United Kingdom.
(3)End TB Dx Consulting LLC, San Diego, California, USA.
(4)DLD IVD Consulting LLC, Medway, Massachusetts, USA.
(5)Molecular and Experimental Mycobacteriology, Research Center Borstel, Borstel, Germany.
(6)German Center for Infection Research, Partner site Hamburg-Lübeck-Borstel-Riems, Borstel, Germany.
(7)Department of Genetics, University of Cambridge, Cambridge, United Kingdom.
(#)Contributed equally

Thirteen commercial genotypic antimicrobial susceptibility assays interrogate mutations upstream of ahpC to infer isoniazid resistance for Mycobacterium tuberculosis. We demonstrate that relying on one of these compensatory mutations (i.e., ahpC c-54t)-rather than causative resistance mutations in katG that ahpC compensates for-can result in systematic false-resistant results for isoniazid with the Cepheid Xpert MTB/XDR and suboptimal treatment. The WHO mutation catalog should be refined to address this scenario.

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Recent TB News

New Initiative Expands Access To Life Saving Drug-Resistant Tuberculosis Treatment
With the new $7.3 million Unitaid investment, Partners In Health (PIH) is launching a new initiative to improve care and quality of life for people suffering from drug-resistant tuberculosis (DR-TB). One project in particular, the Accelerating Regimens and Care for DR-TB (arcTB), will focus on the testing and treatment sides of DR-TB.
https://www.pih.org/press/new-initiative-expands-access-life-saving-drug-resistant-tuberculosis-treatment

TB Experts Rally Around New, Shortened TB Treatments
A regional training session for 20 countries has been successfully completed in Lima, Peru convened by PeerLINC, a global knowledge hub for tuberculosis. Within the training session, participants received guidance ranging from national implementation planning to community engagement practices, with the goal of helping to accelerate the implementation of the WHO-recommended DR-TB treatments.
https://www.tballiance.org/tb-experts-rally-around-new-shortened-tb-treatments/