PubMed Open Access:

1. Tuberculosis treatment-shortening.

Drug Discov Today. 2024 May;29(5):103955. doi: 10.1016/j.drudis.2024.103955. Epub 2024 Mar 26.

Singh V(1).

Author information:
(1)Holistic Drug Discovery and Development (H3D) Centre, University of Cape Town, Rondebosch 7701, South Africa; South African Medical Research Council Drug Discovery and Development Research Unit, University of Cape Town, Rondebosch 7701, South Africa; Institute of Infectious Disease and Molecular Medicine (IDM), University of Cape Town, Observatory 7925, South Africa. Electronic address: vinayak.singh@uct.ac.za.

Tuberculosis (TB) presents a significant global health concern, with ∼10 million people developing TB and 1.3 million people dying from the disease each year. The standard treatment regimen for drug-susceptible TB was between 6 and 9 months until recently, presenting a prolonged therapeutic duration compared with other infectious diseases. This is a long time for patients to adhere to the medication, consequently increasing the risk of developing drug-resistant Mycobacterium tuberculosis - a significant challenge in TB management globally. Therefore, the primary objective of contemporary TB drug development research is to shorten the treatment duration. This review comprehensively explores the strategies aimed at shortening TB treatment.

DOI: 10.1016/j.drudis.2024.103955
PMID: 38548262 [Indexed for MEDLINE]

2. Multidrug-resistant tuberculosis: latest opinions on epidemiology, rapid diagnosis and management.

Curr Opin Pulm Med. 2024 May 1;30(3):217-228. doi: 10.1097/MCP.0000000000001070. Epub 2024 Mar 15.

Nyasulu PS(1)(2), Doumbia CO(3), Ngah V(1), Togo ACG(3), Diarra B(3), Chongwe G(4).

Author information:
(1)Department of Global Health, Faculty of Medicine & Health Sciences, Stellenbosch University, Stellenbosch.
(2)School of Public Health, Faculty of Health Sciences, University of the

Witwatersrand, Johannesburg, South Africa.
(3)University Clinical Research Center, University of Sciences, Techniques and Technologies of Bamako, Bamako, Mali.
(4)Tropical Diseases Research Centre, Ndola, Zambia.

PURPOSE OF REVIEW: This review addresses the escalating global challenge of multidrug-resistant tuberculosis (MDR-TB) in Sub-Saharan Africa, with a focus on its complex comorbidity with HIV/AIDS. Emphasizing the urgency of the issue, the review aims to shed light on the unique healthcare landscape shaped by the convergence of high prevalence rates and intersecting complexities with HIV/AIDS in the region.
RECENT FINDINGS: A notable increase in MDR-TB cases across Sub-Saharan Africa is attributed to challenges in timely diagnoses, treatment initiation, and patient treatment defaulting. The literature underscores the critical need for proactive measures to address diagnostic and treatment gaps associated with MDR-TB, particularly concerning its comorbidity with HIV/AIDS.
SUMMARY: To effectively manage MDR-TB and its co-morbidity with HIV/AIDS, proactive screening programs are imperative. The review highlights the necessity of active follow-up strategies to ensure treatment adherence and reduce default rates, offering evidence-based insights for improved disease management in the region.

DOI: 10.1097/MCP.0000000000001070
PMCID: PMC11095862
PMID: 38488133 [Indexed for MEDLINE]

Conflict of interest statement: There are no conflicts of interest.

3. Drug-resistant Mycobacterium tuberculosis among Nepalese patients at a tuberculosis referral center.

PLoS One. 2024 May 6;19(5):e0301210. doi: 10.1371/journal.pone.0301210. eCollection 2024.

Chand AB(1)(2)(3), Basnet A(2), Maharjan B(3), Rai G(2), Joshi YP(4), Bhatt LR(1), Sen B(5), Rai SK(2)(6).

Author information:
(1)Department of Microbiology, KIST Medical College and Teaching Hospital, Lalitpur, Nepal.
(2)Department of Medical Microbiology, Shi-Gan International College of Science and Technology, Kathmandu, Nepal.
(3)German Nepal Tuberculosis Project, Kathmandu, Nepal.
(4)Department of Public Health, Manmohan Memorial Institute of Health Sciences,

Kathmandu, Nepal.
(5)Department of Dentistry, KIST Medical College and Teaching Hospital, Lalitpur, Nepal.
(6)Department of Microbiology, Nepal Medical College Teaching Hospital, Kathmandu, Nepal.

BACKGROUND: Multidrug-resistant tuberculosis (MDR-TB), characterized by isoniazid and rifampicin resistance, is caused by chromosomal mutations that restrict treatment options and complicate tuberculosis management. This study sought to investigate the prevalence of pre-extensively drug-resistant (pre-XDR) and extensively drug-resistant (XDR) tuberculosis, as well as mutation pattern, in Nepalese patients with MDR/rifampicin-resistant (RR)-TB strains.
METHODS: A cross-sectional study was conducted on MDR/RR-TB patients at the German Nepal Tuberculosis Project from June 2017 to June 2018. The MTBDRsl line probe assay identified pre-XDR-TB and XDR-TB. Pre-XDR-TB included MDR/RR-TB with resistance to any fluoroquinolone (FLQ), while XDR-TB included MDR/RR-TB with resistance to any FLQ and at least one additional group A drug. Mutation status was determined by comparing bands on reaction zones [gyrA and gyrB for FLQ resistance, rrs for SILD resistance, and eis for low-level kanamycin resistance, according to the GenoType MTBDRsl VER 2.0, Hain Lifescience GmbH, Nehren, Germany definition of pre-XDR and XDR] to the evaluation sheet. SPSS version 17.0 was used for data analysis.
RESULTS: Out of a total of 171 patients with MDR/RR-TB, 160 had (93.57%) had MTBC, of whom 57 (35.63%) had pre-XDR-TB and 10 (6.25%) had XDR-TB. Among the pre-XDR-TB strains, 56 (98.25%) were FLQ resistant, while 1 (1.75%) was SLID resistant. The most frequent mutations were found at codons MUT3C (57.14%, 32/56) and MUT1 (23.21%, 13/56) of the gyrA gene. One patient had SLID resistant genotype at the MUT1 codon of the rrs gene (100%, 1/1). XDR-TB mutation bands were mostly detected on MUT1 (30%, 3/10) of the gyrA and rrs, MUT3C (30%, 3/10) of the gyrA, and MUT1 (30%, 3/10) of the rrs.
CONCLUSIONS: Pre-XDR-TB had a significantly higher likelihood than XDR-TB, with different specific mutation bands present in gyrA and rrs genes.

DOI: 10.1371/journal.pone.0301210
PMCID: PMC11073693
PMID: 38709710 [Indexed for MEDLINE]

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

4. Multidrug-resistant tuberculosis in children: A practical update on epidemiology, diagnosis, treatment and prevention.

J Clin Tuberc Other Mycobact Dis. 2024 May 1;36:100449. doi: 10.1016/j.jctube.2024.100449. eCollection 2024 Aug.

Gaensbauer JT(1)(2), Dash N(3), Verma S(4), Hall DJ(5), Adler-Shohet FC(6), Li G(2), Lee G(7), Dinnes L(7), Wendorf K(8).

Author information:
(1)Mayo Clinic Center for Tuberculosis, Mayo Clinic, Rochester, MN, USA.
(2)Division of Pediatric Infectious Diseases, Department of Pediatrics and Adolescent Medicine, Mayo Clinic, Rochester, MN, USA.
(3)Department of Telemedicine, Postgraduate Institute of Medical Education and Research, Chandigarh, India.
(4)Division of Pediatric Infectious Diseases, Department of Pediatrics, Postgraduate Institute of Medical Education and Research, Chandigarh, India.
(5)Division of Pediatric Hospital Medicine, Department of Pediatrics and Adolescent Medicine, Mayo Clinic, Rochester, MN, USA.
(6)Division of Pediatric Infectious Diseases, Department of Pediatrics, Harbor-UCLA Medical Center, Torrance, CA, USA.
(7)Department of Pharmacy, Mayo Clinic, Rochester, MN, USA.
(8)Department of Pediatrics, University of California San Francisco Benioff Children's Hospital, Oakland, CA, USA.

Pediatric multidrug-resistant tuberculosis (MDR-TB) remains a significant global problem, and there are numerous barriers preventing children with MDR-TB from being identified, confirmed with microbiologic tests, and treated with a safe, practical, and effective regimen. However, several recent advances in diagnostics and treatment regimens have the promise to improve outcomes for children with MDR-TB. We introduce this review with two cases that exemplify both the challenges in management of MDR-TB in children, but also the potential to achieve a positive outcome. More than 30,000 cases of MDR-TB per year are believed to occur in children but less than 5% are confirmed microbiologically, contributing to poorer outcomes and excess mortality. Rapid molecular-based testing that provides information on rifampin susceptibility is increasingly globally available and recommended for all children suspected of TB disease--but remains limited by challenges obtaining appropriate samples and the paucibacillary nature of most pediatric TB. More complex assays allowing better characterization of drug-resistant isolates are emerging. For children diagnosed with MDR-TB, treatment regimens have traditionally been long and utilize multiple drugs associated with significant side effects, particularly injectable agents. Several new or repurposed drugs including bedaquiline, delamanid, clofazimine and linezolid now allow most treatment regimens to be shorter and all-oral. Yet data to support short, all-oral, novel regimens for young children containing pretomanid remain insufficient at present, and there is a compelling

need to conduct pediatric trials of promising therapeutics and MDR-TB treatment regimens.

DOI: 10.1016/j.jctube.2024.100449
PMCID: PMC11096739
PMID: 38757115

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.

5. Transmission of fluoroquinolones resistance among multidrug-resistant tuberculosis in Shanghai, China: a retrospective population-based genomic epidemiology study.

Emerg Microbes Infect. 2024 Dec;13(1):2302837. doi: 10.1080/22221751.2024.2302837. Epub 2024 Jan 22.

Li M(1), Zhang Y(2)(3)(4), Wu Z(2)(3), Jiang Y(2)(3), Sun R(1), Yang J(5), Li J(2)(3), Lin H(1), Zhang R(1), Jiang Q(6), Wang L(2)(3), Wu X(5), Yu F(5), Yuan J(7), Yang C(1)(7), Shen X(2)(3).

Author information:
(1)School of Public Health (Shenzhen), Shenzhen Campus of Sun Yat-sen University, Sun Yat-sen University, Guangdong, People's Republic of China.
(2)Division of TB and HIV/AIDS Prevention, Shanghai Municipal Center for Disease Control and Prevention, Shanghai, People's Republic of China.
(3)Shanghai Institutes of Preventive Medicine, Shanghai, People's Republic of China.
(4)Department of Epidemiology, School of Public Health and Key Laboratory of Public Health Safety, Fudan University, Shanghai, People's Republic of China.
(5)Department of Clinical Laboratory, Shanghai Pulmonary Hospital, School of Medicine, Tongji University, Shanghai, People's Republic of China.
(6)Department of Epidemiology and Biostatistics, School of Public Health, Wuhan University, Wuhan, People's Republic of China.
(7)Nanshan District Center for Disease Control and Prevention, Shenzhen, People's Republic of China.

Fluoroquinolones (FQ) are essential for the treatment of multidrug-resistant tuberculosis (MDR-TB). The FQ resistance (FQ-R) rate in MDR-TB in China and its risk factors remain poorly understood. We conducted a retrospective, population-based genomic epidemiology study of MDR-TB patients in Shanghai, China, from 2009 to 2018. A genomic cluster was defined as strains with genetic distances ≤ 12 single nucleotide polymorphisms. The transmitted FQ-R was defined

as the same FQ resistance-conferring mutations shared by ≥ 2 strains in a genomic cluster. We used multivariable logistic regression analysis to identify the risk factors for drug resistance. Among the total 850 MDR-TB patients included in the study, 72.8% (619/850) were male, the median age was 39 (interquartile range 28, 55) years, 52.7% (448/850) were migrants, and 34.5% (293/850) were previously treated patients. Most of the MDR-TB strains belong to the Beijing lineage (91.7%, 779/850). Overall, the genotypic resistance rate of FQ was 34.7% (295/850), and 47.1% (139/295) FQ-R patients were in genomic clusters, of which 98 (33.2%, 98/295) were presumed as transmitted FQ-R. Patients with treatment-naïve (aOR = 1.84; 95% CI: 1.09, 3.16), diagnosed in a district-level hospital (aOR = 2.69; 95% CI: 1.56, 4.75), and streptomycin resistance (aOR = 3.69; 95% CI: 1.65, 9.42) were significantly associated with the transmission of FQ-R. In summary, the prevalence of FQ-R among MDR-TB patients was high in Shanghai, and at least one-third were transmitted. Enforced interventions including surveillance of FQ drug susceptibility testing and screening among MDR-TB before initiation of treatment were urgently needed.

DOI: 10.1080/22221751.2024.2302837
PMCID: PMC10810664
PMID: 38205528 [Indexed for MEDLINE]

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

6. Relationship between HIV viral suppression and multidrug resistant tuberculosis treatment outcomes.

PLOS Glob Public Health. 2024 May 6;4(5):e0002714. doi: 10.1371/journal.pgph.0002714. eCollection 2024.

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

Author information:
(1)School of Nursing, Johns Hopkins University, Baltimore, Maryland, United States of America.
(2)Center for Infectious Disease and Nursing Innovation, Johns Hopkins University, Baltimore, Maryland, United States of America.
(3)Division of Infectious Diseases, Vanderbilt University Medical Center, Nashville, Tennessee, United States of America.
(4)National Department of Health, Tuberculosis Control and Management, Pretoria, Gauteng, South Africa.
(5)KwaZulu-Natal Department of Health, Tuberculosis Programme, Pietermaritzburg, KwaZulu-Natal, South Africa.

The impact of HIV viral suppression on multidrug resistant tuberculosis (MDR-TB)

treatment outcomes among people with HIV (PWH) has not been clearly established. Using secondary data from a cluster-randomized clinical trial among people with MDR-TB in South Africa, we examined the effects of HIV viral suppression at MDR-TB treatment initiation and throughout treatment on MDR-TB outcomes among PWH using multinomial regression. This analysis included 1479 PWH. Viral suppression (457, 30.9%), detectable viral load (524, 35.4%), or unknown viral load (498, 33.7%) at MDR-TB treatment initiation were almost evenly distributed. Having a detectable HIV viral load at MDR-TB treatment initiation significantly increased risk of death compared to those virally suppressed (relative risk ratio [RRR] 2.12, 95% CI 1.11-4.07). Among 673 (45.5%) PWH with a known viral load at MDR-TB outcome, 194 (28.8%) maintained suppression, 267 (39.7%) became suppressed, 94 (14.0%) became detectable, and 118 (17.5%) were never suppressed. Those who became detectable (RRR 11.50, 95% CI 1.98-66.65) or were never suppressed (RRR 9.28, 95% CI 1.53-56.61) were at significantly increased risk of death (RRR 6.37, 95% CI 1.58-25.70), treatment failure (RRR 4.54, 95% CI 1.35-15.24), and loss to follow-up (RRR 7.00, 95% CI 2.83-17.31; RRR 2.97, 95% CI 1.02-8.61) compared to those who maintained viral suppression. Lack of viral suppression at MDR-TB treatment initiation and failure to achieve or maintain viral suppression during MDR-TB treatment drives differences in MDR-TB outcomes. Early intervention to support access and adherence to antiretroviral therapy among PWH should be prioritized to improve MDR-TB treatment outcomes.

DOI: 10.1371/journal.pgph.0002714
PMCID: PMC11073678
PMID: 38709764

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

7. Genotypic and phenotypic drug resistance patterns of Mycobacterium tuberculosis isolated from presumptive pulmonary tuberculosis patients in Ethiopia: A multicenter study.

PLoS One. 2024 May 16;19(5):e0303460. doi: 10.1371/journal.pone.0303460. eCollection 2024.

Yenew B(1)(2), Kebede A(3)(4), Alemu A(1), Diriba G(1), Mehammed Z(1), Amare M(1), Dagne B(1), Sinshaw W(1), Tesfaye E(1), Beyene D(3), Abegaz WE(2).

Author information:
(1)Ethiopian Public Health Institute, Addis Ababa, Ethiopia.

(2)Department of Microbiology, Immunology and Parasitology, College of Health Sciences, Addis Ababa University, Addis Ababa, Ethiopia.
(3)Department of Microbial, Cellular and Molecular Biology, College of Natural and Computational Sciences, Addis Ababa University, Addis Ababa, Ethiopia.
(4)Africa Centres for Disease Control and Prevention, Addis Ababa, Ethiopia.

BACKGROUND: The emergence of drug-resistant tuberculosis (DR-TB) has been a major obstacle to global tuberculosis control programs, especially in developing countries, including Ethiopia. This study investigated drug resistance patterns and associated mutations of Mycobacterium tuberculosis Complex (MTBC) isolates from the Amhara, Gambella, and Benishangul-Gumuz regions of Ethiopia.
METHODS: A cross-sectional study was conducted using 128 MTBC isolates obtained from patients with presumptive tuberculosis (TB). Phenotypic (BACTEC MGIT 960) and genotypic (MTBDRplus and MTBDRsl assays) methods were used for drug susceptibility testing. Data were entered into Epi-info and analyzed using SPSS version 25. Frequencies and proportions were determined to describe drug resistance levels and associated mutations.
RESULTS: Of the 127 isolates recovered, 100 (78.7%) were susceptible to four first-line anti-TB drugs. Any drug resistance, polydrug resistance, and multi-drug resistance (MDR) were detected in 21.3% (27), 15.7% (20), and 15% (19) of the isolates, respectively, by phenotypic and/or genotypic methods. Mono-resistance was observed for Isoniazid (INH) (2, 1.6%) and Streptomycin (STR) (2, 1.6%). There were two genotypically discordant RIF-resistant cases and one INH-resistant case. One case of pre-extensively drug-resistant TB (pre-XDR-TB) and one case of extensively drug-resistant TB (XDR-TB) were identified. The most frequent gene mutations associated with INH and rifampicin (RIF) resistance were observed in the katG MUT1 (S315T1) (20, 76.9%) and rpoB (S531L) (10, 52.6%) genes, respectively. Two MDR-TB isolates were resistant to second-line drugs; one had a mutation in the gyrA MUT1 gene, and the other had missing gyrA WT1, gyrA WT3, and rrs WT1 genes without any mutation.
CONCLUSIONS: The detection of a significant proportion of DR-TB cases in this study suggests that DR-TB is a major public health problem in Ethiopia. Thus, we recommend the early detection and treatment of DR-TB and universal full first-line drug-susceptibility testing in routine system.

DOI: 10.1371/journal.pone.0303460
PMCID: PMC11098317
PMID: 38753615 [Indexed for MEDLINE]

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

8. Transmission characteristics in Tuberculosis by WGS: nationwide cross-sectional surveillance in China.

Emerg Microbes Infect. 2024 Dec;13(1):2348505. doi: 10.1080/22221751.2024.2348505. Epub 2024 May 15.

Liu D(1), Huang F(2), Li Y(3), Mao L(4), He W(2), Wu S(4), Xia H(2), He P(2), Zheng H(5), Zhou Y(2), Zhao B(2), Ou X(2), Song Y(2), Song Z(2), Mei L(1), Liu L(1), Zhang G(6), Wei Q(1), Zhao Y(2).

Author information:
(1)National Pathogen Resource Center, Chinese Center for Disease Control and Prevention, Beijing, People's Republic of China.
(2)National Tuberculosis Reference Laboratory, National Center for Tuberculosis Control and Prevention, Chinese Center for Disease Control and Prevention, Beijing, People's Republic of China.
(3)Department of Nutrition, Beijing Friendship Hospital, Capital Medical University.
(4)Joint Research Center for Molecular Diagnosis of Severe Infection in Children, Binjiang Institute of Zhejiang University, Hangzhou, People's Republic of China.
(5)Laboratory of Respiratory Diseases, Beijing Key Laboratory of Pediatric Respiratory Infection Diseases, Beijing Pediatric Research Institute, Beijing Children's Hospital, Capital Medical University, Key Laboratory of Major Diseases in Children, Ministry of Education, National Clinical Research Center for Respiratory Diseases, National Center for Children's Health, Beijing, People's Republic of China.
(6)National Clinical Research Center for Infectious Diseases, Guangdong Clinical Research Center for Tuberculosis, Shenzhen Third People's Hospital, Shenzhen, People's Republic of China.

China, with the third largest share of global tuberculosis cases, faces a substantial challenge in its healthcare system as a result of the high burden of multidrug-resistant and rifampicin-resistant tuberculosis (MDR/RR-TB). This study employs a genomic epidemiological approach to assess recent tuberculosis transmissions between individuals, identifying potential risk factors and discerning the role of transmitted resistant isolates in the emergence of drug-resistant tuberculosis in China. We conducted a population-based retrospective study on 5052 Mycobacterium tuberculosis (MTB) isolates from 70 surveillance sites using whole genome sequencing (WGS). Minimum spanning tree analysis identified resistance mutations, while epidemiological data analysis pinpointed transmission risk factors. Of the 5052 isolates, 23% (1160) formed 452 genomic clusters, with 85.6% (387) of the transmissions occurring within the same counties. Individuals with younger age, larger family size, new cases, smear positive, and MDR/RR were at higher odds for recent transmission, while

higher education (university and above) and occupation as a non-physical workers emerged as protective factors. At least 61.4% (251/409) of MDR/RR-TB were likely a result of recent transmission of MDR/RR isolates, with previous treatment (crude OR = 2.77), smear-positive (cOR = 2.07) and larger family population (cOR = 1.13) established as risk factors. Our findings highlight that local transmission remains the predominant form of TB transmission in China. Correspondingly, drug-resistant tuberculosis is primarily driven by the transmission of resistant tuberculosis isolates. Targeted interventions for high-risk populations to interrupt transmission within the country will likely provide an opportunity to reduce the prevalence of both tuberculosis and drug-resistant tuberculosis.

DOI: 10.1080/22221751.2024.2348505
PMCID: PMC11097701
PMID: 38686553 [Indexed for MEDLINE]

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

9. Genomic analysis of lineage-specific transmission of multidrug resistance tuberculosis in China.

Emerg Microbes Infect. 2024 Dec;13(1):2294858. doi: 10.1080/22221751.2023.2294858. Epub 2024 Feb 13.

Li YF(1), Kong XL(2), Song WM(3), Li YM(4)(5), Li YY(4)(5), Fang WW(4), Yang JY(4), Yu CB(6), Li HC(4), Liu Y(4).

Author information:
(1)Department of Respiratory and Critical Care Medicine, The Third Affiliated Hospital of Shandong First Medical University, Jinan, People's Republic of China.
(2)Shandong Artificial Intelligence Institute Qilu University of Technology (Shandong Academy of Sciences), Jinan, People's Republic of China.
(3)Department of Respiratory Medicine, Ruijin Hospital Affiliated to Shanghai Jiaotong University, Shanghai, People's Republic of China.
(4)Department of Respiratory and Critical Care Medicine, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, People's Republic of China.
(5)Department of Respiratory and Critical Care Medicine, Shandong University of Traditional Chinese Medicine, Jinan, People's Republic of China.
(6)Center for Integrative and Translational Medicine, Shandong Public Health Clinical Center, Jinan, People's Republic of China.

OBJECTIVES: We investigated the genetic diversities and lineage-specific transmission dynamics of multidrug-resistant tuberculosis (MDR-TB), with the

goal of determining the potential factors driving the MDR epidemics in China.
METHODS: We curated a large nationwide Mycobacterium tuberculosis (M. tuberculosis) whole genome sequence data set, including 1313 MDR strains. We reconstructed the phylogeny and mapped the transmission networks of MDR-TB across China using Bayesian inference. To identify drug-resistance variants linked to enhanced transmissibility, we employed ordinary least-squares (OLS) regression analysis.
RESULT: The majority of MDR-TB strains in China belong to lineage 2.2.1. Transmission chain analysis has indicated that the repeated and frequent transmission of L2.2.1 plays a central role in the establishment of MDR epidemic in China, but no occurrence of a large predominant MDR outbreak was detected. Using OLS regression, the most common single nucleotide polymorphisms (SNPs) associated with resistance to isoniazid (katG_p.Ser315Thr and katG_p.Ser315Asn) and rifampicin (rpoB_p.Ser450Leu, rpoB_p.His445Tyr, rpoB_p.His445Arg, rpoB_p.His445Asp, and rpoB_p.His445Asn) were more likely to be found in L2 clustered strains. Several putative compensatory mutations in rpoA, rpoC, and katG were significantly associated with clustering. The eastern, central, and southern regions of China had a high level of connectivity for the migration of L2 MDR strains throughout the country. The skyline plot showed distinct population size expansion dynamics for MDR-TB lineages in China.
CONCLUSION: MDR-TB epidemic in China is predominantly driven by the spread of highly transmissible Beijing strains. A range of drug-resistance mutations of L2 MDR-TB strains displayed minimal fitness costs and may facilitate their transmission.

DOI: 10.1080/22221751.2023.2294858
PMCID: PMC10866052
PMID: 38126135 [Indexed for MEDLINE]

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

10. Epidemiology of first- and second-line drugs-resistant pulmonary tuberculosis in Iran: Systematic review and meta-analysis.

J Clin Tuberc Other Mycobact Dis. 2024 Mar 16;35:100430. doi: 10.1016/j.jctube.2024.100430. eCollection 2024 May.

Abbasian S(1), Heidari H(2), Abbasi Tadi D(3), Kardan-Yamchi J(4), Taji A(5), Darbandi A(6), Asadollahi P(7), Maleki A(7), Kazemian H(7).

Author information:
(1)Laboratory Sciences Research Center, Golestan University of Medical Sciences, Gorgan, Iran.
(2)Department of Microbiology, Faculty of Medicine, Shahid Sadoughi University of Medical Sciences, Yazd, Iran.

(3)Department of Veterinary, Azad University of Shahr-e Kord, Shahr-e Kord, Iran.
(4)Quality Control and Screening Management Office, Deputy of Technical and New Technologies, Iranian Blood Transfusion Organization, Tehran, Iran.
(5)International Campus, Shahid Sadoughi University of Medical Sciences, Yazd, Iran.
(6)Department of Microbiology, Faculty of Medicine, Iran University of Medical Sciences, Tehran, Iran.
(7)Clinical Microbiology Research Center, Ilam University of Medical Sciences, Ilam, Iran.

Drug resistance among Mycobacterium tuberculosis (MTB) strains is a growing concern in developing countries. We conducted a comprehensive search for relevant studies in Iran on PubMed, Scopus, and Embase until June 12, 2020. Our study focused on determining the prevalence of antibiotic resistance in MTB isolates, with subgroup analyses based on year, location, and drug susceptibility testing (DST) methods. Statistical analyses were performed using STATA software. Our meta-analysis included a total of 47 articles. Among new TB cases, we found the following prevalence rates: Any-resistance to first-line drugs: 31 % (95 % CI, 24-38), mono-drug resistance: 15 % (95 % CI, 10-22), and multidrug resistance to first-line drugs: 6 % (95 % CI, 4-8). There was a significant variation in the rate of MDR among new TB cases based on the year of publication, location, and DST methods ($P < 0.0001$). We observed substantial variability in multidrug-resistant TB rates among new cases across the studies. Stratified analyses revealed that publication years and DST methods significantly affected resistance rates. Studies from southern and central Iran reported higher any-drug resistance rates, suggesting regional differences. Among retreatment cases, the prevalence rates were as follows: Any resistance: 68 % (95 % CI 58-78), mono-resistance: 19 % (95 % CI 7-34), multidrug resistance: 28 % (95 % CI 15-43). Our study revealed that the prevalence of drug-resistant TB (DR-TB) among TB cases in Iran is higher than the global average. Particularly, MDR-TB among retreatment TB cases is a significant public health issue.

DOI: 10.1016/j.jctube.2024.100430
PMCID: PMC10981085
PMID: 38560029

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. Role of therapeutic drug monitoring in the treatment of multi-drug resistant

tuberculosis.

J Clin Tuberc Other Mycobact Dis. 2024 Apr 24;36:100444. doi: 10.1016/j.jctube.2024.100444. eCollection 2024 Aug.

Maranchick NF(1)(2), Peloquin CA(1)(2).

Author information:
(1)Infectious Disease Pharmacokinetics Lab, Department of Pharmacotherapy and Translational Research, College of Pharmacy, University of Florida, Gainesville, FL, USA.
(2)Emerging Pathogens Institute, University of Florida, Gainesville, FL, USA.

Tuberculosis (TB) is a leading cause of mortality worldwide, and resistance to anti-tuberculosis drugs is a challenge to effective treatment. Multi-drug resistant TB (MDR-TB) can be difficult to treat, requiring long durations of therapy and the use of second line drugs, increasing a patient's risk for toxicities and treatment failure. Given the challenges treating MDR-TB, clinicians can improve the likelihood of successful outcomes by utilizing therapeutic drug monitoring (TDM). TDM is a clinical technique that utilizes measured drug concentrations from the patient to adjust therapy, increasing likelihood of therapeutic drug concentrations while minimizing the risk of toxic drug concentrations. This review paper provides an overview of the TDM process, pharmacokinetic parameters for MDR-TB drugs, and recommendations for dose adjustments following TDM.

DOI: 10.1016/j.jctube.2024.100444
PMCID: PMC11067344
PMID: 38708036

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.

12. Prevalence of Drug-Resistant Tuberculosis in HIV-Positive and Diabetic Patients in Sinaloa, Mexico: A Retrospective Cross-Sectional Study.

Trop Med Infect Dis. 2024 Apr 22;9(4):89. doi: 10.3390/tropicalmed9040089.

Aispuro Pérez A(1), Osuna-Martínez U(1), Espinoza-Gallardo JA(2), Dorantes-Álvarez LA(2), Inzunza-Leyva GK(2), Dorantes-Bernal KE(2), Quiñonez-Bastidas GN(3).

Author information:

(1)Facultad de Ciencias Químico-Biológicas, Universidad Autónoma de Sinaloa, Ciudad Universitaria, Culiacan 80013, Sinaloa, Mexico.
(2)Coordinación Estatal de Tuberculosis, Servicios de Salud de Sinaloa, Secretaria de Salud Blvd, Alfonso Zaragoza Maytorena No. 2204, Fraccionamiento Bonanzas, Culiacan 80020, Sinaloa, Mexico.
(3)Centro de Investigación y Docencia en Ciencias de la Salud, Universidad Autónoma de Sinaloa, Eustaquio Buelna 91, Burocrata, Culiacan 80030, Sinaloa, Mexico.

Tuberculosis (TB) is a disease caused by the bacillus Mycobacterium tuberculosis (MTB). Human immunodeficiency virus (HIV) infection and type 2 diabetes mellitus (T2DM) are among the main risk factors for the development of TB and increase the risk of drug-resistant TB developing (DR-TB). The aim of this study was to estimate the prevalence of DR-TB in patients with HIV or T2DM in Sinaloa, Mexico. This was an observational and cross-sectional study. The analysis was conducted using the clinical data of patients registered on the National Epidemiological Surveillance System for TB (SINAVE/PUI-TB) platform with a presumed diagnosis of TB during 2019 to 2021 in Sinaloa, Mexico. The prevalence of DR-TB was estimated in HIV and T2DM patients, as well as the odds ratios for their sociodemographic variables, using the Chi-square test. There were 2, 4, and 4 TB-HIV cases and 2, 6, and 9 TB-T2DM cases during 2019, 2020, and 2021, respectively, whereas there were 2 and 1 DRTB-HIV and DRTB-T2DM cases, respectively. The results indicated that the WHO guidelines for DR-TB were not properly applied to this high-risk population. Hence, the appropriate application of guidelines for TB and DR-TB detection in these patients needs to be immediately implemented by the State health system.

DOI: 10.3390/tropicalmed9040089
PMCID: PMC11054973
PMID: 38668550

Conflict of interest statement: The authors declare that they have no conflicts of interest. Espinosa-Gallardo, Dorantes-Alvarez, Inzunza-Leyva and Dorantes-Bernal have working relationships with the Services of Health in Sinaloa; they did not receive payment or any other retribution for their participation in this study.

13. Telemedicine as a tool to prevent multi-drug resistant tuberculosis in poor resource settings: Lessons from Nigeria.

J Clin Tuberc Other Mycobact Dis. 2024 Feb 24;35:100423. doi: 10.1016/j.jctube.2024.100423. eCollection 2024 May.

Olowoyo KS(1)(2), Esan DT(3), Adeyanju BT(4), Olawade DB(5), Oyinloye BE(6), Olowoyo P(7).

Author information:
(1)Department of Nursing Science, College of Medicine and Health Sciences, Afe Babalola University, Ado-Ekiti, Nigeria.
(2)Department of Internal Medicine, Ekiti State University Teaching Hospital, Ado-Ekiti, Nigeria.
(3)Faculty of Nursing Sciences, College of Health Sciences, Bowen University, Iwo, Nigeria.
(4)Department of Obstetrics and Gynecology, Afe Babalola University/ABUAD Multi-System Hospital, Ado-Ekiti, Nigeria.
(5)Department of Allied and Public Health, School of Health, Sport and Bioscience, University of East London, London, United Kingdom.
(6)Department of Biochemistry, College of Sciences, Afe Babalola University, Ado-Ekiti, Nigeria and Department of Biochemistry and Microbiology, University of Zululand, KwaDlangezwa, South Africa.
(7)Department of Internal Medicine, Federal Teaching Hospital Ido-Ekiti, Nigeria/Afe Babalola University, Ado-Ekiti, Nigeria.

BACKGROUND: This mini review aims to provide an overview of the role of telemedicine in preventing multi-drug resistant tuberculosis (MDR-TB) in Nigeria. The specific objectives include examining the potential benefits of telemedicine, identifying the challenges associated with its implementation, and highlighting the importance of addressing infrastructure limitations and data privacy concerns.
METHODS: This minireview is based on a comprehensive analysis of existing literature, including scholarly articles, and reports,. A systematic search was conducted using electronic databases, such as PubMed and Google Scholar, to identify relevant publications related to telemedicine and MDR-TB prevention in Nigeria. The selected articles were assessed for their relevance, and key findings were synthesized to provide an overview of the role of telemedicine in addressing the challenges of MDR-TB in Nigeria.
RESULTS: The review demonstrates that telemedicine has the potential to significantly contribute to MDR-TB prevention efforts in Nigeria. The benefits of telemedicine include improved access to specialized care, enhanced patient adherence to treatment, and potential cost savings. However, challenges such as infrastructure limitations and data privacy concerns need to be addressed for successful implementation. Integrating telemedicine into the healthcare system has the potential to strengthen MDR-TB prevention, particularly in underserved areas, including within Nigeria. Specifically, the integration of telemedicine into the healthcare system can enhance access to specialized care, improve patient adherence, and potentially reduce costs associated with MDR-TB management.
CONCLUSIONS: Addressing infrastructure challenges, ensuring data privacy and security, and fostering trust among healthcare providers and patients are critical for successful implementation of telemedicine. Further research and policy frameworks are needed to guide the effective implementation and scale-up of telemedicine in MDR-TB prevention efforts in Nigeria.

DOI: 10.1016/j.jctube.2024.100423
PMCID: PMC10907208
PMID: 38435000

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.

14. Rifampicin resistant Mycobacterium tuberculosis in Vietnam, 2020-2022.

J Clin Tuberc Other Mycobact Dis. 2024 Mar 15;35:100431. doi: 10.1016/j.jctube.2024.100431. eCollection 2024 May.

Van Nguyen H(1)(2), Binh Nguyen H(1), Thu Ha D(1), Thi Huong D(1), Ngoc Trung V(1), Thi Thuy Ngoc K(1), Huyen Trang T(1), Vu Thi Ngoc H(3), Trinh Thi Bich T(3), Le Pham Tien T(3), Nguyen Hong H(3), Phan Trieu P(3), Kim Lan L(3), Lan K(3), Ngoc Hue N(3), Thi Le Huong N(3), Le Thi Ngoc Thao T(3), Le Quang N(3), Do Dang Anh T(3), Hữu Lân N(4), Van Vinh T(4), Thi Minh Ha D(4), Thuong Dat P(4), Phuc Hai N(4), Crook DW(5)(6), Thuy Thuong Thuong N(3)(6), Viet Nguyen N(2), Thwaites GE(3)(6), Walker TM(3)(6).

Author information:
(1)National Lung Hospital, Hanoi, Viet Nam.
(2)Vietnam National University, University of Medicine and Pharmacy, Viet Nam.
(3)Oxford University Clinical Research Unit, Ho Chi Minh City, Viet Nam.
(4)Pham Ngoc Thach Hospital, Ho Chi Minh City, Viet Nam.
(5)Nuffield Department of Medicine, University of Oxford, Oxford, UK.
(6)Centre for Tropical Medicine and Global Health, Nuffield Department of Medicine, University of Oxford, Oxford, UK.

OBJECTIVE: We conducted a descriptive analysis of multi-drug resistant tuberculosis (MDR-TB) in Vietnam's two largest cities, Hanoi and Ho Chi Minh city.
METHODS: All patients with rifampicin resistant tuberculosis were recruited from Hanoi and surrounding provinces between 2020 and 2022. Additional patients were recruited from Ho Chi Minh city over the same time period. Demographic data were recorded from all patients, and samples collected, cultured, whole genome sequenced and analysed for drug resistance mutations. Genomic susceptibility predictions were made on the basis of the World Health Organization's catalogue of mutations in Mycobacterium tuberculosis associated with drug resistance, version 2. Comparisons were made against phenotypic drug susceptibility test results where these were available. Multivariable logistic regression was used to assess risk factors for previous episodes of tuberculosis.

RESULTS: 233/265 sequenced isolates were of sufficient quality for analysis, 146 (63 %) from Ho Chi Minh City and 87 (37 %) from Hanoi. 198 (85 %) were lineage 2, 20 (9 %) were lineage 4, and 15 (6 %) were lineage 1. 17/211 (8 %) for whom HIV status was known were infected, and 109/214 (51 %) patients had had a previous episode of tuberculosis. The main risk factor for a previous episode was HIV infection (odds ratio 5.1 (95 % confidence interval 1.3-20.0); p = 0.021). Sensitivity for predicting first-line drug resistance from whole genome sequencing data was over 90 %, with the exception of pyrazinamide (85 %). For moxifloxacin and amikacin it was 50 % or less. Among rifampicin-resistant isolates, prevalence of resistance to each non-first-line drug was < 20 %. CONCLUSIONS: Drug resistance among most MDR-TB strains in Vietnam's two largest cities is confined largely to first-line drugs. Living with HIV is the main risk factor among patients with MDR-TB for having had a previous episode of tuberculosis.

DOI: 10.1016/j.jctube.2024.100431
PMCID: PMC10958107
PMID: 38523706

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.

15. Determinants of multidrug-resistant tuberculosis among adults undergoing treatment for tuberculosis in Tigray Region, Ethiopia: a case-control study.

BMJ Open Respir Res. 2024 May 2;11(1):e001999. doi: 10.1136/bmjresp-2023-001999.

Zereabruk K(1), Kahsay T(2), Teklemichael H(2), Aberhe W(3), Hailay A(3), Mebrahtom G(3), Bezabh G(2).

Author information:
(1)Adult health Nursing, Aksum University College of Health Science and Medicine, Axum, Ethiopia zereabrukkidane@gmail.com.
(2)Nursing, Mekelle University College of Health Sciences, Mekelle, Tigray, Ethiopia.
(3)Adult health Nursing, Aksum University College of Health Science and Medicine, Axum, Ethiopia.

BACKGROUND: Multidrug-resistant tuberculosis is a type of tuberculosis that is resistant to at least the first-line antituberculosis drugs namely, rifampicin and isoniazid. However, most of these studies were limited only to a single hospital. Therefore, this study aimed to identify the determinants of multidrug-resistant tuberculosis among adults undergoing treatment for

tuberculosis in the Tigray region of Ethiopia.
METHODS: Hospital-based unmatched case-control study was conducted from 1 April 2019 to 30 June 2019. A simple random sampling method was used to select the required sample size. Variables at a p value less than 0.25 in bivariate analysis were entered into a multivariable analysis to identify the determinant factors of multidrug-resistant tuberculosis. Finally, the level of significance was declared at $p<0.05$.
RESULTS: Rural residence (adjusted OR (AOR) 2.54; 95% CI 1.34 to 4.83), HIV (AOR 4.5; 95% CI 1.4 to 14.2), relapse (AOR 3.86; 95% CI 1.98 to 7.5), return after lost follow-up (AOR 6.29; 95% CI 1.64 to 24.2), treatment failure (AOR 5.87; 95% CI 1.39 to 24.8) were among the determinants of multidrug-resistant tuberculosis.
CONCLUSION: Rural residence, HIV, relapses, return after lost follow-up and treatment failure were the identified determinant factors of multidrug-resistance tuberculosis.

DOI: 10.1136/bmjresp-2023-001999
PMCID: PMC11086502
PMID: 38697676 [Indexed for MEDLINE]

Conflict of interest statement: Competing interests: None declared.

16. Transmission of drug-resistant Mycobacterium tuberculosis isolates between Finnish- and foreign-born cases, 2014-2021: A molecular epidemiological study.

Tuberculosis (Edinb). 2024 May;146:102492. doi: 10.1016/j.tube.2024.102492. Epub 2024 Feb 12.

Zhu J(1), Haanpera M(2), Mentula S(2), Vapalahti O(3), Soini H(2), Sironen T(3), Kant R(4), Zakham F(3).

Author information:
(1)Department of Virology, University of Helsinki, Helsinki, Finland. Electronic address: jiahui.zhu@helsinki.fi.
(2)Department of Health Security, Finnish Institute for Health and Welfare, Helsinki, Finland.
(3)Department of Virology, University of Helsinki, Helsinki, Finland; Department of Basic Veterinary Sciences, Faculty of Veterinary Medicine, University of Helsinki, Helsinki, Finland.
(4)Department of Virology, University of Helsinki, Helsinki, Finland; Department of Basic Veterinary Sciences, Faculty of Veterinary Medicine, University of Helsinki, Helsinki, Finland; Department of Tropical Parasitology, Institute of Maritime and Tropical Medicine, Medical University of Gdansk, Gdynia, Poland.

BACKGROUND: Data on the molecular epidemiology and transmission of drug-resistant Mycobacterium tuberculosis (MTB) in low-incidence settings with immigration from high-incidence settings is limited.
METHOD: We included 115 drug-resistant (DR) MTB isolates with whole-genome sequencing data isolated in Finland between 2014 and 2021. Potential transmission clusters were identified using a threshold of 12 single-nucleotide polymorphisms (SNPs). Highly related clusters were identified using a threshold of 5 SNPs.
RESULT: Of the 115 DR MTB isolates, 31 (27.0%) isolates were from Finnish-born cases and 84 (73.0%) were from foreign-born cases. The proportion of multidrug-resistant (MDR) MTB isolates (30/84, 35.7%) from foreign-born cases was higher than that of MDR MTB isolates from Finnish-born cases (8/31, 25.8%). Lineage 2 (40/115, 34.8%) and lineage 4 (40/115, 34.8%) were the most prevalent lineages. A total of 25 (21.7%) isolates were classified into eight potential transmission clusters (≤12 SNPs). Furthermore, five highly related clusters (≤5 SNPs) were identified, including three DR MTB isolates from Finnish-born cases and 14 DR isolates from foreign-born cases.
CONCLUSION: The risk of DR MTB transmission between Finnish- and foreign-born persons is not negligible. Further research on clustering analysis in drug-susceptible MTB is worth to inform tuberculosis management and control in low-incidence settings with increasing immigration.

DOI: 10.1016/j.tube.2024.102492
PMID: 38364331 [Indexed for MEDLINE]

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

17. Concomitant bedaquiline and delamanid therapy in patients with drug-resistant extra-pulmonary tuberculosis in Mumbai, India.

J Clin Tuberc Other Mycobact Dis. 2024 Apr 1;35:100433. doi: 10.1016/j.jctube.2024.100433. eCollection 2024 May.

Mongia H(1), Mamnoon F(1), Silsarma A(1), Mahajan R(1), Dalal A(2), Galindo MA(1), Iyer A(1), Singh P(1), Mansoor H(1), Das M(1), Morales M(1), Spencer H(3), Isaakidis P(3)(4).

Author information:
(1)Médecins Sans Frontières, Mumbai, India.
(2)Jupiter Hospital, Mumbai, India.

(3)Southern Africa Medical Unit, Médecins Sans Frontières, Cape Town, South Africa.
(4)Clinical and Molecular Epidemiology Unit, Department of Hygiene and Epidemiology, University of Ioannina School of Medicine, Ioannina, Greece.

BACKGROUND: World Health Organization suggests concurrent bedaquiline-delamanid (BDQ-DLM) as part of individualised regimens for eligible patients with pulmonary drug-resistant tuberculosis (DR-TB); however, data for patients with drug-resistant extrapulmonary tuberculosis (EPTB) is extremely limited. This study documents the treatment outcomes and adverse events associated with concurrent BDQ-DLM-based regimens in patients with drug-resistant EPTB at a Médecins Sans Frontières clinic in Mumbai, India.
METHODS: Retrospective cohort study based on routinely collected programmatic data. Individualised regimens were based on drug-susceptibility testing and previous drug exposure. Drug-resistant EPTB patients initiated on regimens containing concurrent BDQ and DLM from April 2016 to October 2019 were included. Patients who completed treatment were followed up at 12 months.
RESULTS: Of 17 patients, median age was 23 years (IQR = 21-30 years) and 12/17 (71 %) were female. Pre-extensively drug-resistant tuberculosis and extensively drug-resistant TB was reported in 13/17 (76.4 %) and 2/17 (11.7 %) patients respectively. Microbiological reports were unavailable for two patients with central nervous system TB. Lymph node TB was the commonest form of EPTB in 9/17 (53 %) of patients. Median duration of treatment was 18.9 months. At least one grade three or four severe adverse event (SAE) was reported by 13/17 (76.4 %) patients. Thirteen (76.4 %) patients had favourable outcomes. None of the patients relapsed or died in the one-year period of post-treatment follow-up.
CONCLUSION: Concurrent BDQ-DLM-based regimens in drug-resistant EPTB were effective and associated with manageable adverse events.

DOI: 10.1016/j.jctube.2024.100433
PMCID: PMC11015490
PMID: 38617837

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.

18. Low body mass index as a predictor of sputum culture conversion and treatment outcomes among patients receiving treatment for multidrug-resistant tuberculosis in Lesotho.

Glob Health Action. 2024 Dec 31;17(1):2305930. doi: 10.1080/16549716.2024.2305930. Epub 2024 Feb 2.

Oyewusi L(1), Zeng C(2), Seung KJ(3), Mpinda S(1), Kunda M(1), Mitnick CD(2), Kanu M(1), Tamirat M(1), Makaka J(1), Mofolo M(1), Maime R(1), Maama L(4), Senyo N(1), Oguntoyinbo B(1), Mayombo L(1), Franke MF(2).

Author information:
(1)Clinical department (MDRTB), Partners In Health, Maseru, Lesotho.
(2)Department of Global Health and Social Medicine, Harvard Medical School, Boston, MA, USA.
(3)Division of Global Health Equity, Brigham and Women's Hospital, Boston, MA, USA.
(4)National TB and Leprosy Programme, Lesotho Ministry of Health, Maseru, Lesotho.

BACKGROUND: A low body mass index (BMI) at the start of treatment for rifampicin- or multidrug-resistant tuberculosis (MDR/RR-TB) is associated with poor treatment outcomes and may contribute to delayed sputum culture conversion, thereby prolonging the period of potential transmission to others. Whether the relative importance of low BMI in predicting treatment outcomes differs by HIV status is unclear.
OBJECTIVES: We evaluated the association between low BMI and two dependent variables, sputum culture conversion and end-of-treatment outcome, among patients receiving treatment for MDR/RR-TB in Lesotho, a setting with a high prevalence of HIV infection.
METHODS: Secondary data from a prospective cohort of patients initiating a longer (18-20 months) treatment containing bedaquiline and/or delamanid under routine programmatic conditions in Lesotho were analysed. Risk ratios and differences were adjusted for potential confounders using multivariable logistic regression, and estimates were stratified by HIV status.
RESULTS: Of 264 patients, 105 and 250 were eligible for culture conversion and end-of-treatment analyses, respectively. Seventy-one per cent of patients (74/105) experienced culture conversion within six months, while 74% (184/250) experienced a favourable end-of-treatment outcome. Low BMI was associated with a lower frequency of culture conversion at six months among those who were not living with HIV (relative risk [RR]: 0.50 [95% CI: 0.21, 0.79]); this association was attenuated among those living with HIV (RR: 0.88 [95% CI: 0.68, 1.23]). A low BMI was moderately associated with a lower frequency of treatment success (RR = 0.89 [95% CI: 0.77, 1.03]), regardless of HIV status.
CONCLUSIONS: Low BMI was common and associated with the frequency of six-month culture conversion and end-of-treatment outcomes. The association with culture conversion was more pronounced among those not living with HIV. Addressing the myriad factors that drive low BMI in this setting could hasten culture conversion and improve end-of-treatment outcomes. This will require a multipronged approach focused on alleviating food insecurity and enabling prompt diagnosis and treatment of HIV and TB.

DOI: 10.1080/16549716.2024.2305930

PMCID: PMC10840591
PMID: 38305025 [Indexed for MEDLINE]

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

19. Impact and cost-effectiveness of the 6-month BPaLM regimen for rifampicin-resistant tuberculosis in Moldova: A mathematical modeling analysis.

PLoS Med. 2024 May 3;21(5):e1004401. doi: 10.1371/journal.pmed.1004401. eCollection 2024 May.

James LP(1)(2), Klaassen F(3), Sweeney S(4), Furin J(5), Franke MF(5), Yaesoubi R(6), Chesov D(7)(8), Ciobanu N(9), Codreanu A(9), Crudu V(9), Cohen T(10), Menzies NA(2)(3).

Author information:
(1)PhD Program in Health Policy, Harvard University, Cambridge, Massachusetts, United States of America.
(2)Center for Health Decision Science, Harvard T. H. Chan School of Public Health, Boston, Massachusetts, United States of America.
(3)Department of Global Health and Population, Harvard T. H. Chan School of Public Health, Boston, Massachusetts, United States of America.
(4)Faculty of Public Health and Policy, London School of Hygiene and Tropical Medicine, London, United Kingdom.
(5)Department of Global Health and Social Medicine, Harvard Medical School, Boston, Massachusetts, United States of America.
(6)Department of Health Policy and Management, Yale School of Public Health, New Haven, Connecticut, United States of America.
(7)Discipline of Pneumology and Allergology, Nicolae Testemitanu State University of Medicine and Pharmacy, Chișinău, Moldova.
(8)Clinical Infectious Diseases, Research Center Borstel, Borstel, Germany.
(9)Chiril Draganiuc Institute of Phthisiopneumology, Chișinău, Moldova.
(10)Department of Epidemiology and Microbial Diseases, Yale School of Public Health, New Haven, Connecticut, United States of America.

BACKGROUND: Emerging evidence suggests that shortened, simplified treatment regimens for rifampicin-resistant tuberculosis (RR-TB) can achieve comparable end-of-treatment (EOT) outcomes to longer regimens. We compared a 6-month regimen containing bedaquiline, pretomanid, linezolid, and moxifloxacin (BPaLM) to a standard of care strategy using a 9- or 18-month regimen depending on whether fluoroquinolone resistance (FQ-R) was detected on drug susceptibility testing (DST).
METHODS AND FINDINGS: The primary objective was to determine whether 6 months of BPaLM is a cost-effective treatment strategy for RR-TB. We used genomic and demographic data to parameterize a mathematical model estimating long-term

health outcomes measured in quality-adjusted life years (QALYs) and lifetime costs in 2022 USD ($) for each treatment strategy for patients 15 years and older diagnosed with pulmonary RR-TB in Moldova, a country with a high burden of TB drug resistance. For each individual, we simulated the natural history of TB and associated treatment outcomes, as well as the process of acquiring resistance to each of 12 anti-TB drugs. Compared to the standard of care, 6 months of BPaLM was cost-effective. This strategy was estimated to reduce lifetime costs by $3,366 (95% UI: [1,465, 5,742] $p < 0.001$) per individual, with a nonsignificant change in QALYs (-0.06; 95% UI: [-0.49, 0.03] $p = 0.790$). For those stopping moxifloxacin under the BPaLM regimen, continuing with BPaL plus clofazimine (BPaLC) provided more QALYs at lower cost than continuing with BPaL alone. Strategies based on 6 months of BPaLM had at least a 93% chance of being cost-effective, so long as BPaLC was continued in the event of stopping moxifloxacin. BPaLM for 6 months also reduced the average time spent with TB resistant to amikacin, bedaquiline, clofazimine, cycloserine, moxifloxacin, and pyrazinamide, while it increased the average time spent with TB resistant to delamanid and pretomanid. Sensitivity analyses showed 6 months of BPaLM to be cost-effective across a broad range of values for the relative effectiveness of BPaLM, and the proportion of the cohort with FQ-R. Compared to the standard of care, 6 months of BPaLM would be expected to save Moldova's national TB program budget $7.1 million (95% UI: [1.3 million, 15.4 million] $p = 0.002$) over the 5-year period from implementation. Our analysis did not account for all possible interactions between specific drugs with regard to treatment outcomes, resistance acquisition, or the consequences of specific types of severe adverse events, nor did we model how the intervention may affect TB transmission dynamics.
CONCLUSIONS: Compared to standard of care, longer regimens, the implementation of the 6-month BPaLM regimen could improve the cost-effectiveness of care for individuals diagnosed with RR-TB, particularly in settings with a high burden of drug-resistant TB. Further research may be warranted to explore the impact and cost-effectiveness of shorter RR-TB regimens across settings with varied drug-resistant TB burdens and national income levels.

DOI: 10.1371/journal.pmed.1004401
PMCID: PMC11101189
PMID: 38701084 [Indexed for MEDLINE]

Conflict of interest statement: JF has received grant funding from the Stop TB Partnership’s Global Drug Facility to support the roll out of child-friendly formulations of second-line TB drugs.

20. Mitigating treatment failure of pulmonary pre-extensively drug-resistant tuberculosis: The role of new and repurposed drugs.

J Microbiol Immunol Infect. 2024 Apr 26:S1684-1182(24)00076-8. doi: 10.1016/j.jmii.2024.04.008. Online ahead of print.

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

Author information:
(1)Chang-Hua Hospital, Ministry of Health and Welfare, Chang-Hua, Taiwan; Institute of Medicine, Chang Shan Medical University, Taichung, Taiwan.
(2)Division of Pulmonary Medicine, Department of Internal Medicine, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan; School of Respiratory Therapy, College of Medicine, Taipei Medical University, Taipei, Taiwan.
(3)Division of Chest Medicine, Department of Internal Medicine, Tzu Chi General Hospital, Tzu Chi University, Hualien, Taiwan; School of Medicine, Tzu Chi University, Hualien, Taiwan.
(4)Division of Chest Medicine, Department of Internal Medicine, Tzu Chi General Hospital, Tzu Chi University, Hualien, Taiwan.
(5)Tao-Yuan General Hospital, Ministry of Health and Welfare, Tao-Yuan, Taiwan.
(6)Chest Hospital, Ministry of Health and Welfare, Tainan, Taiwan.
(7)Division of Pulmonary Medicine, Department of Internal Medicine, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan; Department of Internal Medicine, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan.
(8)Division of Pulmonary Medicine, Department of Internal Medicine, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan; Department of Internal Medicine, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan; International Union Against Tuberculosis and Lung Disease, Paris, France. Electronic address: cychiang@theunion.org.

BACKGROUND: Pre-extensively drug-resistant tuberculosis (pre-XDR-TB), defined as multidrug-resistant TB (MDR-TB) with additional resistance to any fluoroquinolone (FQ) is difficult to treat. We assessed whether the use of new or repurposed drugs (bedaquiline, delamanid, linezolid, carbapenem, clofazimine, pretomanid) mitigated treatment failure of pre-XDR-TB.
METHODS: MDR-TB patients managed in the Taiwan MDR-TB consortium between July 2009-December 2019 were eligible. Treatment outcomes at 30 months were assessed. Logistic regression models were constructed to investigate factors associated with treatment outcomes.
RESULTS: 109 patients with FQ-resistant MDR-TB and 218 patients with FQ-susceptible MDR-TB were included. 60 (55.1%) patients with FQ-resistant MDR-TB and 63 (28.9%) patients with FQ-susceptible MDR-TB have been treated with new or repurposed drugs ($p < 0.01$). Of the 218 patients with FQ-susceptible

MDR-TB, 187 (85.8%) had treatment success, 30 (13.8%) died, no treatment failure, and 1 (0.5%) was loss-to-follow-up; of the 109 patients with FQ-resistant MDR-TB, 78 (71.6%) had treatment success, 21 (19.3%) died, 9 (8.3%) had treatment failure, and 1 (0.9%) was loss-to-follow-up ($p < 0.01$). The use of new or repurposed drugs was not associated with treatment outcomes among patients with FQ-susceptible MDR-TB. No patients with FQ-resistant MDR-TB treated with ≥2 new or repurposed drugs within 6 months of treatment initiation had treatment failure ($p = 0.03$). Patients with FQ-resistant MDR-TB treated with 1 new or repurposed drugs was more likely to have treatment failure as compared with patients not treated with new or repurposed drugs (adjOR 7.06, 95% CI 1.72-29.06).
CONCLUSIONS: Proper use of new or repurposed anti-TB drugs can mitigate treatment failure in FQ-resistant MDR-TB.

DOI: 10.1016/j.jmii.2024.04.008
PMID: 38705821

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

21. Rifampicin tolerance and growth fitness among isoniazid-resistant clinical Mycobacterium tuberculosis isolates: an in-vitro longitudinal study.

bioRxiv [Preprint]. 2024 May 4:2023.11.22.568240. doi: 10.1101/2023.11.22.568240.

Vijay S, Bao NLH, Vinh DN, Nhat LTH, Thu DDA, Quang NL, Trieu LPT, Nhung HN, Ha VTN, Thai PVK, Ha DTM, Lan NH, Caws M, Thwaites GE, Javid B, Thuong NTT.

Antibiotic tolerance in Mycobacterium tuberculosis leads to less effective bacterial killing, poor treatment responses and resistant emergence. Therefore, we investigated the rifampicin tolerance of M. tuberculosis isolates, with or without pre-existing isoniazid-resistance. We determined the in-vitro rifampicin survival fraction by minimum duration of killing assay in isoniazid susceptible (IS, n=119) and resistant (IR, n=84) M. tuberculosis isolates. Then we correlated the rifampicin tolerance with bacterial growth, rifampicin minimum inhibitory concentrations (MICs) and isoniazid-resistant mutations. The longitudinal IR isolates collected from patients were analyzed for changes in rifampicin tolerance and associated emergence of genetic variants. The median duration of rifampicin exposure reducing the M. tuberculosis surviving fraction by 90% (minimum duration of killing-MDK90) increased from 1.23 (95%CI 1.11; 1.37) and 1.31 (95%CI 1.14; 1.48) to 2.55 (95%CI 2.04; 2.97) and 1.98 (95%CI 1.69; 2.56) days, for IS and IR respectively, during 15 to 60 days of incubation. This indicated the presence of fast and slow growing tolerant sub-populations. A range of 6 log 10 -fold survival fraction enabled

classification of tolerance as low, medium or high and revealed IR association with increased tolerance with faster growth (OR=2.68 for low vs. medium, OR=4.42 for low vs. high, P -trend=0.0003). The high tolerance in IR isolates was specific to those collected during rifampicin treatment in patients and associated with bacterial genetic microvariants. Furthermore, the high rifampicin tolerant IR isolates have survival potential similar to multi-drug resistant isolates. These findings suggest that IR tuberculosis needs to be evaluated for high rifampicin tolerance to improve treatment regimen and prevent the risk of MDR-TB emergence.

DOI: 10.1101/2023.11.22.568240
PMCID: PMC10690245
PMID: 38045287

22. Assessing potential drug-drug interactions between clofazimine and other frequently used agents to treat drug-resistant tuberculosis.

Antimicrob Agents Chemother. 2024 May 2;68(5):e0158323. doi: 10.1128/aac.01583-23. Epub 2024 Apr 10.

Kengo A(#)(1), Nabeemeeah F(#)(2), Denti P(1), Sabet R(2), Okyere-Manu G(2), Abraham P(2), Weisner L(1), Mosala MH(2), Tshabalala S(3), Scholefield J(3), Resendiz-Galvan JE(#)(1), Martinson NA(#)(2)(4), Variava E(#)(2)(5).

Author information:
(1)Division of Clinical Pharmacology, Department of Medicine, University of Cape Town, Cape Town, South Africa.
(2)Perinatal HIV Research Unit (PHRU), University of the Witwatersrand, Johannesburg, South Africa.
(3)Bioengineering and Integrated Genomics Group, Council for Scientific and Industrial Research, Pretoria, South Africa.
(4)Johns Hopkins University Center for Tuberculosis Research, Division of Infectious Diseases, School of Medicine, Baltimore, Maryland, USA.
(5)Department of Internal Medicine, University of the Witwatersrand, Klerksdorp/Tshepong Hospital Complex North-West Province, Klerksdorp-Tshepong, South Africa.
(#)Contributed equally

Clofazimine is included in drug regimens to treat rifampicin/drug-resistant tuberculosis (DR-TB), but there is little information about its interaction with other drugs in DR-TB regimens. We evaluated the pharmacokinetic interaction between clofazimine and isoniazid, linezolid, levofloxacin, and cycloserine, dosed as terizidone. Newly diagnosed adults with DR-TB at Klerksdorp/Tshepong Hospital, South Africa, were started on the then-standard treatment with clofazimine temporarily excluded for the initial 2 weeks. Pharmacokinetic sampling was done immediately before and 3 weeks after starting clofazimine, and

drug concentrations were determined using validated liquid chromatography-tandem mass spectrometry assays. The data were interpreted with population pharmacokinetics in NONMEM v7.5.1 to explore the impact of clofazimine co-administration and other relevant covariates on the pharmacokinetics of isoniazid, linezolid, levofloxacin, and cycloserine. Clofazimine, isoniazid, linezolid, levofloxacin, and cycloserine data were available for 16, 27, 21, 21, and 6 participants, respectively. The median age and weight for the full cohort were 39 years and 52 kg, respectively. Clofazimine exposures were in the expected range, and its addition to the regimen did not significantly affect the pharmacokinetics of the other drugs except levofloxacin, for which it caused a 15% reduction in clearance. A posteriori power size calculations predicted that our sample sizes had 97%, 90%, and 87% power at $P < 0.05$ to detect a 30% change in clearance of isoniazid, linezolid, and cycloserine, respectively. Although clofazimine increased the area under the curve of levofloxacin by 19%, this is unlikely to be of great clinical significance, and the lack of interaction with other drugs tested is reassuring.

DOI: 10.1128/aac.01583-23
PMCID: PMC11064479
PMID: 38597667 [Indexed for MEDLINE]

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

23. Incidence, Outcomes, and Risk Factors for Isoniazid-Resistant Tuberculosis from 2012 to 2022 in Eastern China.

Antibiotics (Basel). 2024 Apr 22;13(4):378. doi: 10.3390/antibiotics13040378.

Shao Y(1), Song W(2), Song H(1), Li G(1), Zhu L(1), Liu Q(1), Chen C(1).

Author information:
(1)Center for Disease Control and Prevention of Jiangsu Province, Department of Chronic Communicable Disease, Nanjing 210009, China.
(2)Center for Disease Control and Prevention of Kunshan, Suzhou 215300, China.

BACKGROUND: Isoniazid-resistant, rifampicin-susceptible tuberculosis (Hr-TB) is the most frequent drug-resistant tuberculosis (DR-TB) in the world, and unfavorable outcomes of Hr-TB are more common compared to drug-susceptible TB. Considering there is no optimal regimen accepted worldwide, we undertook a retrospective cohort study in eastern China to estimate incidence trends and risk factors associated with unfavorable outcomes of Hr-TB.
METHODS: Between January 2012 and December 2022, all Hr-TB patients' information was extracted from the Tuberculosis Information Management System (TIMS), which is a national electronic information platform, to record TB patients' clinical information in this study. The incidence of Hr-TB was determined by the mid-year population according to census data published by the government. We categorized

treatment regimens depending on fluoroquinolone (FQ) use, and potential risk factors were analyzed using multivariable logistic regression.
RESULTS: A total of 3116 Hr-TB patients fulfilled the inclusion criteria and were enrolled in this study. The average annual rate of Hr-TB in the 11 years under investigation was 0.34 per 100,000 and increased to 0.53 per 100,000 until 2019. In total, six different treatment regimens were utilized in the study sites, and less than 1% of regimens adopted FQ. There was no difference in the unfavorable outcomes between the FQ-included and FQ-excluded groups ($p = 0.22$). The average treatment duration was 7.06 months, and the longest treatment was 26 months. Approximately 20% (637/3116) of Hr-TB patients had unfavorable outcomes, and 60.13% (383/637) of them proceeded to multidrug-resistant tuberculosis (MDR-TB). Treatment duration and a positive smear at the end of the 5th month were significantly associated with unfavorable outcomes ($p < 0.001$).
CONCLUSION: The unfavorable treatment outcomes of Hr-TB are still high in eastern China, and the efficacy of FQ-containing regimens needs to be validated for Hr-TB treatment.

DOI: 10.3390/antibiotics13040378
PMCID: PMC11047343
PMID: 38667054

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

24. Delineating the evolutionary pathway to multidrug-resistant outbreaks of a Mycobacterium tuberculosis L4.1.2.1/Haarlem sublineage.

Int J Infect Dis. 2024 Apr 30:107077. doi: 10.1016/j.ijid.2024.107077. Online ahead of print.

Dekhil N(1), Mardassi H(2).

Author information:
(1)Unit of Typing & Genetics of Mycobacteria, Laboratory of Molecular Microbiology, Vaccinology, and Biotechnology Development, Institut Pasteur de Tunis, Université de Tunis El Manar, Tunis, Tunisia.
(2)Unit of Typing & Genetics of Mycobacteria, Laboratory of Molecular Microbiology, Vaccinology, and Biotechnology Development, Institut Pasteur de Tunis, Université de Tunis El Manar, Tunis, Tunisia. Electronic address: helmi.mardassi@mesrs.tn.

OBJECTIVES: We sought to capture the evolutionary itinerary of the Mycobacterium tuberculosis L4.1.2.1/Haarlem sublineage, northern Tunisia, where it caused a major multidrug-resistant (MDR-TB) outbreak, in a context strictly negative for HIV infection.
METHODS: We combined whole genome sequencing and Bayesian approaches using a representative collection of drug-susceptible and drug-resistant

L4.1.2.1/Haarlem clinical strains (n =121) recovered from the outbreak region over 16 years.
RESULTS: In the absence of drug resistance, the L4.1.2.1/Haarlem sublineage showed a propensity for rapid transmission as witnessed by the high clustering (44.6%) and recent transmission rates (25%), as well as the reduced mean distance between genome pairs. The entire pool of L4.1.2.1/Haarlem MDR strains was found to be linked to either the aforementioned major outbreak (68 individuals, 2001-2016) or to a minor, newly uncovered outbreak (6 cases, 2001-2011). Strikingly, the two outbreaks descended independently from a common ancestor that can be dated back to 1886.
CONCLUSION: Our data point to the intrinsic propensity for rapid transmission of the M. tuberculosis L4.1.2.1/Haarlem sublineage in northern Tunisia, linking the overall MDR-TB epidemic to a single ancestor. These findings bring out the important role of the bacillus's genetic background in the emergence of successful MDR M. tuberculosis clones.

DOI: 10.1016/j.ijid.2024.107077
PMID: 38697608

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.

25. Pharmacokinetics and pharmacodynamics of high-dose isoniazid for the treatment of rifampicin- or multidrug-resistant tuberculosis in Indonesia.

J Antimicrob Chemother. 2024 May 2;79(5):977-986. doi: 10.1093/jac/dkae057.

Yunivita V(1)(2), Gafar F(1)(3)(4), Santoso P(5), Chaidir L(2)(6), Soeroto AY(5), Meirina TN(7), Te Brake L(8), Menzies D(3)(4), Aarnoutse RE(8), Ruslami R(1)(2)(4).

Author information:
(1)Division of Pharmacology and Therapy, Department of Biomedical Sciences, Faculty of Medicine, Universitas Padjadjaran, Bandung, Indonesia.
(2)TB Working Group, Research Center for Care and Control of Infectious Diseases, Universitas Padjadjaran, Bandung, Indonesia.
(3)Respiratory Epidemiology and Clinical Research Unit, Centre for Outcomes Research and Evaluation, Research Institute of the McGill University Health Centre, 5252 Boulevard de Maisonneuve Ouest, Office 3D.21, Montreal, Quebec H4A 3S5, Canada.
(4)McGill International TB Centre, McGill University, Montreal, Quebec, Canada.
(5)Division of Respirology and Critical Care, Department of Internal Medicine,

Faculty of Medicine, Universitas Padjadjaran and Hasan Sadikin General Hospital, Bandung, Indonesia.
(6)Division of Microbiology, Department of Biomedical Sciences, Faculty of Medicine, Universitas Padjadjaran, Bandung, Indonesia.
(7)Pharmacokinetic Laboratory, Faculty of Medicine, Universitas Padjadjaran, Bandung, Indonesia.
(8)Department of Pharmacy, Radboud Institute for Medical Innovation, Radboud university medical center, Nijmegen, the Netherlands.

BACKGROUND: Pharmacokinetic data on high-dose isoniazid for the treatment of rifampicin-/multidrug-resistant tuberculosis (RR/MDR-TB) are limited. We aimed to describe the pharmacokinetics of high-dose isoniazid, estimate exposure target attainment, identify predictors of exposures, and explore exposure-response relationships in RR/MDR-TB patients.
METHODS: We performed an observational pharmacokinetic study, with exploratory pharmacokinetic/pharmacodynamic analyses, in Indonesian adults aged 18-65 years treated for pulmonary RR/MDR-TB with standardized regimens containing high-dose isoniazid (10-15 mg/kg/day) for 9-11 months. Intensive pharmacokinetic sampling was performed after ≥2 weeks of treatment. Total plasma drug exposure (AUC0-24) and peak concentration (Cmax) were assessed using non-compartmental analyses. AUC0-24/MIC ratio of 85 and Cmax/MIC ratio of 17.5 were used as exposure targets. Multivariable linear and logistic regression analyses were used to identify predictors of drug exposures and responses, respectively.
RESULTS: We consecutively enrolled 40 patients (median age 37.5 years). The geometric mean isoniazid AUC0-24 and Cmax were 35.4 h·mg/L and 8.5 mg/L, respectively. Lower AUC0-24 and Cmax values were associated ($P<0.05$) with non-slow acetylator phenotype, and lower Cmax values were associated with male sex. Of the 26 patients with MIC data, less than 25% achieved the proposed targets for isoniazid AUC0-24/MIC (n=6/26) and Cmax/MIC (n=5/26). Lower isoniazid AUC0-24 values were associated with delayed sputum culture conversion (>2 months of treatment) [adjusted OR 0.18 (95% CI 0.04-0.89)].
CONCLUSIONS: Isoniazid exposures below targets were observed in most patients, and certain risk groups for low isoniazid exposures may require dose adjustment. The effect of low isoniazid exposures on delayed culture conversion deserves attention.

DOI: 10.1093/jac/dkae057
PMCID: PMC11062943
PMID: 38459759 [Indexed for MEDLINE]

26. Population structure and spatial distribution of Mycobacterium tuberculosis in Ethiopia.

Sci Rep. 2024 May 7;14(1):10455. doi: 10.1038/s41598-024-59435-3.

Getahun M(1), Beyene D(2), Mollalign H(3), Diriba G(3), Tesfaye E(3), Yenew B(3), Taddess M(3), Sinshaw W(3), Ameni G(4)(5).

Author information:
(1)Ethiopian Public Health Institute, P.O. Box 1242, Addis Ababa, Ethiopia. mimishaget@yahoo.com.
(2)Department of Microbial, Cellular and Molecular Biology, Addis Ababa University, Addis Ababa, Ethiopia.
(3)Ethiopian Public Health Institute, P.O. Box 1242, Addis Ababa, Ethiopia.
(4)Aklilu Lemma Institute of Pathobiology, Addis Ababa University, Addis Ababa, Ethiopia.
(5)Department of Veterinary Medicine, College of Agriculture and Veterinary Medicine, United Arab Emirates University, Al Ain, United Arab Emirates.

Ethiopia is one of the countries with a high tuberculosis (TB) burden, yet little is known about the spatial distribution of Mycobacterium tuberculosis (Mtb) lineages. This study identifies the spoligotyping of 1735 archived Mtb isolates from the National Drug Resistance Survey, collected between November 2011 and June 2013, to investigate Mtb population structure and spatial distribution. Spoligotype International Types (SITs) and lineages were retrieved from online databases. The distribution of lineages was evaluated using Fisher's exact test and logistic regression models. The Global Moran's Index and Getis-Ord Gi statistic were utilized to identify hotspot areas. Our results showed that spoligotypes could be interpreted and led to 4 lineages and 283 spoligotype patterns in 91% of the isolates, including 4% of those with multidrug/rifampicin resistance (MDR/RR) TB. The identified Mtb lineages were lineage 1 (1.8%), lineage 3 (25.9%), lineage 4 (70.6%) and lineage 7 (1.6%). The proportion of lineages 3 and 4 varied by regions, with lineage 3 being significantly greater than lineage 4 in reports from Gambella (AOR = 4.37, $P < 0.001$) and Tigray (AOR = 3.44, $P = 0.001$) and lineage 4 being significantly higher in Southern Nations Nationalities and Peoples Region (AOR = 1.97, $P = 0.026$) than lineage 3. Hotspots for lineage 1 were located in eastern Ethiopia, while a lineage 7 hotspot was identified in northern and western Ethiopia. The five prevalent spoligotypes, which were SIT149, SIT53, SIT25, SIT37 and SIT26 account for 42.8% of all isolates under investigation, while SIT149, SIT53 and SIT21 account for 52-57.8% of drug-resistant TB cases. TB and drug resistant TB are mainly caused by lineages 3 and 4, and significant proportions of the prevalent spoligotypes also influence drug-resistant TB and the total TB burden. Regional variations in lineages may result from both local and cross-border spread.

DOI: 10.1038/s41598-024-59435-3

PMCID: PMC11076284
PMID: 38714745 [Indexed for MEDLINE]

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

27. The presence of cytotoxic CD4 and exhausted-like CD8+ T-cells is a signature of active tuberculosis.

Biochim Biophys Acta Mol Basis Dis. 2024 May 9:167219. doi: 10.1016/j.bbadis.2024.167219. Online ahead of print.

Flores-Gonzalez J(1), Ramón-Luing LA(1), Falfán-Valencia R(2), Batista CVF(3), Soto-Alvarez S(3), Huerta-Nuñez L(3), Chávez-Galán L(4).

Author information:
(1)Laboratory of Integrative Immunology, Instituto Nacional de Enfermedades Respiratorias Ismael Cosio Villegas, Mexico City 14080. Mexico.
(2)HLA Laboratory, Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas, Mexico City 14080, Mexico.
(3)Laboratory of Pharmacology, Escuela Militar de Graduados de Sanidad, Universidad del Ejército y Fuerza Aérea Mexicana, Mexico City 11200, Mexico.
(4)Laboratory of Integrative Immunology, Instituto Nacional de Enfermedades Respiratorias Ismael Cosio Villegas, Mexico City 14080. Mexico. Electronic address: lchavez_galan@iner.gob.mx.

Chronic infections induce CD4+ T-cells with cytotoxic functions (CD4 CTLs); at present, it is still unknown whether latent tuberculosis (LTB) and active tuberculosis (ATB) induce CD4 CTLs. Plasma and cells from four patient groups-uninfected contact (UC), LTB, and ATB (divided as sensitive [DS-TB]- or resistant [DR-TB]-drug)-were evaluated by flow cytometry, q-PCR, and proteomics. The data showed that ATB patients had an increased frequency of CD4+ T-cells and a decreased frequency of CD8+ T-cells. The latter displays an exhausted-like profile characterized by CD39, CD279, and TIM-3 expression. ATB had a high frequency of CD4 + perforin+ cells, suggesting a CD4 CTL profile. The expression (at the transcriptional level) of granzyme A, granzyme B, granulysin, and perforin, as well as the genes T-bet (Tbx21) and NKG2D (Klrk1), in enriched CD4+ T-cells, confirmed the cytotoxic signature of CD4+ T-cells during ATB (which was stronger in DS-TB than in DR-TB). Moreover, proteomic analysis revealed the presence of HSP70 (in DS-TB) and annexin A5 (in DR-TB), which are molecules that have been associated with favoring the CD4 CTL profile. Finally, we found that lipids from Mycobacterium tuberculosis increased the presence of CD4 CTLs in DR-TB patients. Our data suggest that ATB is characterized by exhausted-like CD8+ T-cells, which, together with a specific microenvironment, favor the presence of CD4 CTLs.

DOI: 10.1016/j.bbadis.2024.167219
PMID: 38734321

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

28. Effect of Bedaquiline and Delamanid Pharmacokinetics on Sputum Culture Conversion and Adverse Events in Drug-Resistant Tuberculosis.

Ther Drug Monit. 2024 Jun 1;46(3):363-369. doi: 10.1097/FTD.0000000000001164. Epub 2024 Jan 1.

Bhatnagar AK(1), Hemanthkumar AK(2), Muthu Vijayalakshmi M(2), Vohra V(3), Padmapriyadarsini C(2), Ramesh PM(4), Taneja G(1), Chavan VN(5), Jeyadeepa B(2), Bhui NK(5), Solanki R(6).

Author information:
(1)Rajan Babu Institute of Pulmonary Medicine and Tuberculosis, New Delhi.
(2)ICMR-National Institute for Research in Tuberculosis, Chennai.
(3)National Institute for Tuberculosis and Respiratory Diseases, New Delhi.
(4)Government Thiruvatteeswarar Hospital of Thoracic Medicine, Chennai.
(5)Group of TB Hospitals, Mumbai; and.
(6)B.J.Medical College and Hospital, Ahmedabad, India.

BACKGROUND: Pharmacokinetic studies of bedaquiline and delamanid in patients with pre-extensively drug-resistant tuberculosis (pre-XDR TB) will help in the optimization of these drugs for both culture conversion and adverse events.
METHODS: A prospective cohort of 165 adult patients (56% male with mean [SD] age 29 [9.7] years) with pre-XDR TB was treated with bedaquiline, delamanid, clofazimine, and linezolid for 24 weeks at 5 sites in India. Bedaquiline was administered at 400 mg daily for 2 weeks followed by 200 mg thrice weekly for 22 weeks, whereas delamanid was administered at 100 mg twice daily. In 23 consenting participants at 8 and 16 weeks of treatment, blood was collected at 0, 2, 4, 5, 6, 8, 12, and 24 hours postdosing for an intense pharmacokinetic study. Pharmacokinetic parameters were correlated with sputum culture conversion and adverse events.
RESULTS: The mean (SD) age and weight of patients were 30 (10) years and 54 kg, respectively. The median minimum concentration (C min) and time-concentration curve (AUC) for bedaquiline, respectively, were 0.6 mcg/mL and 27 mcg/mL·h at week 8 and 0.8 mcg/mL and 36 mcg/mL·h at week 16, suggesting drug accumulation over time. The median C min and AUC of delamanid, respectively, were 0.17 mcg/mL and 5.1 mcg/mL·h at week 8 and 0.20 mcg/mL and 7.5 mcg/mL·h at week 16. Delay in sputum conversion was observed in patients with drug concentrations lower than

the targeted concentration. At weeks 8 and 16, 13 adverse events were observed. Adverse events were resolved through symptomatic treatment. Body mass index was found to be significantly associated with drug-exposure parameters.
CONCLUSIONS: Bedaquiline and delamanid when co-administered exhibit plasma drug levels within the targeted concentrations, showing an exposure-response relationship.

DOI: 10.1097/FTD.0000000000001164
PMCID: PMC11078291
PMID: 38161267 [Indexed for MEDLINE]

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

29. Concordance of targeted and whole genome sequencing for Mycobacterium tuberculosis genotypic drug susceptibility testing.

Diagn Microbiol Infect Dis. 2024 Jun;109(2):116249. doi: 10.1016/j.diagmicrobio.2024.116249. Epub 2024 Mar 12.

Cloutier Charette W(1), Rabodoarivelo MS(2), Point F(3), Knoblauch AM(4), Andrianomanana FR(5), Hall MB(6), Iqbal Z(6), Supply P(7), Martin A(8), Rakotosamimanana N(5), Grandjean Lapierre S(9).

Author information:
(1)Department of Microbiology, Infectious Diseases and Immunology, Université de Montréal, Montréal, Québec, Canada; Immunopathology Axis, Centre de Recherche du Centre Hospitalier de l'Université de Montréal, Montréal, Québec, Canada.
(2)Mycobacteriology Unit, Institut Pasteur de Madagascar, Antananarivo, Madagascar; Departamento de Microbiología, Medicina Preventiva y Salud Pública, Universidad de Zaragoza, Spain.
(3)Immunopathology Axis, Centre de Recherche du Centre Hospitalier de l'Université de Montréal, Montréal, Québec, Canada.
(4)Swiss Tropical and Public Health Institute, Allschwil, Switzerland; University of Basel, Basel, Switzerland.
(5)Mycobacteriology Unit, Institut Pasteur de Madagascar, Antananarivo, Madagascar.
(6)European Molecular Biology Laboratory, European Bioinformatics Institute, Wellcome Genome Campus, Hinxton, UK.
(7)Univ. Lille, CNRS, Inserm, CHU Lille, Institut Pasteur de Lille, U1019 - UMR 9017 - CIIL - Center for Infection and Immunity of Lille, F-59000 Lille, France.
(8)Institut de Recherche Expérimentale et Clinique, Université Catholique de Louvain, Belgium.

(9)Department of Microbiology, Infectious Diseases and Immunology, Université de Montréal, Montréal, Québec, Canada; Immunopathology Axis, Centre de Recherche du Centre Hospitalier de l'Université de Montréal, Montréal, Québec, Canada; Mycobacteriology Unit, Institut Pasteur de Madagascar, Antananarivo, Madagascar. Electronic address: simon.grandjean.lapierre@umontreal.ca.

Targeted Next Generation Sequencing (tNGS) and Whole Genome Sequencing (WGS) are increasingly used for genotypic drug susceptibility testing (gDST) of Mycobacterium tuberculosis. Thirty-two multi-drugs resistant and 40 drug susceptible isolates from Madagascar were tested with Deeplex® Myc-TB and WGS using the Mykrobe analysis pipeline. Sixty-four of 72 (89 %) yielded concordant categorical gDST results for drugs tested by both assays. Mykrobe didn't detect pncA K96T, pncA Q141P, pncA H51P, pncA H82R, rrs C517T and rpsL K43R mutations, which were identified as minority variants in corresponding isolates by tNGS. One discrepancy (rrs C517T) was associated with insufficient sequencing depth on WGS. Deeplex® Myc-TB didn't detect inhA G-154A which isn't covered by the assay's amplification targets. Despite those targets being included in the Deeplex® Myc-TB assay, a pncA T47A and a deletion in gid were not identified in one isolate respectively. The evaluated WGS and tNGS gDST assays show high but imperfect concordance.

DOI: 10.1016/j.diagmicrobio.2024.116249
PMID: 38537504 [Indexed for MEDLINE]

Conflict of interest statement: Declaration of competing interest The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Philip Supply reports a relationship with GenoScreen that includes: consulting or advisory. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

30. The importance of heteroresistance and efflux pumps in bedaquiline-resistant Mycobacterium tuberculosis isolates from Iran.

Ann Clin Microbiol Antimicrob. 2024 Apr 25;23(1):36. doi: 10.1186/s12941-024-00694-3.

Madadi-Goli N(1)(2)(3), Ahmadi K(1)(2)(4)(3), Kamakoli MK(1)(2), Azizi M(4), Khanipour S(1)(2), Dizaji SP(1)(2), Nasehi M(5)(6), Siadat SD(1)(2), Fateh A(7)(8), Vaziri F(9)(10).

Author information:
(1)Department of Mycobacteriology and Pulmonary Research, Pasteur Institute of

Iran, No. 358, 12th Farvardin Ave., Jomhoori St, Tehran, 1316943551, Iran.
(2)Microbiology Research Center (MRC), Pasteur Institute of Iran, Tehran, Iran.
(3)Student Research Committee, Pasteur Institute of Iran, Tehran, Iran.
(4)Department of Microbiology, School of Medicine, Kermanshah University of Medical Sciences, Kermanshah, Iran.
(5)Department of Epidemiology and Biostatistics, School of Public Health, Iran University of Medical Sciences, Tehran, Iran.
(6)Center for Communicable Diseases Control, Ministry of Health and Medical Education, Tehran, Iran.
(7)Department of Mycobacteriology and Pulmonary Research, Pasteur Institute of Iran, No. 358, 12th Farvardin Ave., Jomhoori St, Tehran, 1316943551, Iran. afateh2@gmail.com.
(8)Microbiology Research Center (MRC), Pasteur Institute of Iran, Tehran, Iran. afateh2@gmail.com.
(9)Department of Mycobacteriology and Pulmonary Research, Pasteur Institute of Iran, No. 358, 12th Farvardin Ave., Jomhoori St, Tehran, 1316943551, Iran. farzam_vaziri@yahoo.com.
(10)Microbiology Research Center (MRC), Pasteur Institute of Iran, Tehran, Iran. farzam_vaziri@yahoo.com.

BACKGROUND: Tuberculosis (TB) continues to pose a threat to communities worldwide and remains a significant public health issue in several countries. We assessed the role of heteroresistance and efflux pumps in bedaquiline (BDQ)-resistant Mycobacterium tuberculosis isolates.
METHODS: Nineteen clinical isolates were included in the study, of which fifteen isolates were classified as MDR or XDR, while four isolates were fully susceptible. To evaluate BDQ heteroresistance, the Microplate Alamar Blue Assay (MABA) method was employed. For screening mixed infections, MIRU-VNTR was performed on clinical isolates. Mutations in the atpE and Rv0678 genes were determined based on next-generation sequencing data. Additionally, real-time PCR was applied to assess the expression of efflux pump genes in the absence and presence of verapamil (VP).
RESULTS: All 15 drug-resistant isolates displayed resistance to BDQ. Among the 19 total isolates, 21.05% (4/19) exhibited a heteroresistance pattern to BDQ. None of the isolates carried a mutation of the atpE and Rv0678 genes associated with BDQ resistance. Regarding the MIRU-VNTR analysis, most isolates (94.73%) showed the Beijing genotype. Fifteen (78.9%) isolates showed a significant reduction in BDQ MIC after VP treatment. The efflux pump genes of Rv0676c, Rv1258c, Rv1410c, Rv1634, Rv1819, Rv2459, Rv2846, and Rv3065 were overexpressed in the presence of BDQ.
CONCLUSIONS: Our results clearly demonstrated the crucial role of heteroresistance and efflux pumps in BDQ resistance. Additionally, we established a direct link between the Rv0676c gene and BDQ resistance. The inclusion of VP significantly reduced the MIC of BDQ in both drug-susceptible and drug-resistant clinical isolates.

DOI: 10.1186/s12941-024-00694-3
PMCID: PMC11046812
PMID: 38664815 [Indexed for MEDLINE]

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

31. Exploring health care providers' engagement in prevention and management of multidrug resistant Tuberculosis and its factors in Hadiya Zone health care facilities: qualitative study.

BMC Health Serv Res. 2024 Apr 27;24(1):542. doi: 10.1186/s12913-024-10911-6.

Lajore BA(#)(1), Aweke YH(#)(2)(3), Ayanto SY(#)(4)(5), Ayele M(6)(7).

Author information:
(1)Department of Family Health, Hossana College of health sciences, Hossana, Ethiopia. bereketema41@gmail.com.
(2)Department of Health informatics, Hossana College of Health Sciences, Hossana, Ethiopia.
(3)College of Health Sciences, School of Public Health, Addis Ababa University, Addis Ababa, Ethiopia.
(4)Department of Midwifery, Hossana College of Health Sciences, Hossana, Ethiopia.
(5)College of Health Sciences, Institute of Public Health, Department of -Population and Family Health, Jimma University, Jimma, Ethiopia.
(6)Department of Clinical Nursing, Hossana College of Health Sciences, Hossana, Ethiopia.
(7)Hossana College of Health Sciences, Hosanna, SNNPR, Ethiopia.
(#)Contributed equally

BACKGROUND: Engagement of healthcare providers is one of the World Health Organization strategies devised for prevention and provision of patient centered care for multidrug resistant tuberculosis. The need for current research question rose because of the gaps in evidence on health professional's engagement and its factors in multidrug resistant tuberculosis service delivery as per the protocol in the prevention and management of multidrug resistant tuberculosis.
PURPOSE: The purpose of this study was to explore the level of health care providers' engagement in multidrug resistant tuberculosis prevention and management and influencing factors in Hadiya Zone health facilities, Southern Ethiopia.
METHODS: Descriptive phenomenological qualitative study design was employed between 02 May and 09 May, 2019. We conducted a key informant interview and focus group discussions using purposely selected healthcare experts working as

directly observed treatment short course providers in multidrug resistant tuberculosis treatment initiation centers, program managers, and focal persons. Verbatim transcripts were translated to English and exported to open code 4.02 for line-by-line coding and categorization of meanings into same emergent themes. Thematic analysis was conducted based on predefined themes for multidrug resistant tuberculosis prevention and management and core findings under each theme were supported by domain summaries in our final interpretation of the results. To maintain the rigors, Lincoln and Guba's parallel quality criteria of trustworthiness was used particularly, credibility, dependability, transferability, confirmability and reflexivity.
RESULTS: Total of 26 service providers, program managers, and focal persons were participated through four focus group discussion and five key informant interviews. The study explored factors for engagement of health care providers in the prevention and management of multidrug resistant tuberculosis in five emergent themes such as patients' causes, perceived susceptibility, seeking support, professional incompetence and poor linkage of the health care facilities. Our findings also suggest that service providers require additional training, particularly in programmatic management of drug-resistant tuberculosis.
CONCLUSION: The study explored five emergent themes: patient's underlying causes, seeking support, perceived susceptibility, professionals' incompetence and health facilities poor linkage. Community awareness creation to avoid fear of discrimination through provision of support for those with multidrug resistant tuberculosis is expected from health care providers using social behavioral change communication strategies. Furthermore, program managers need to follow the recommendations of World Health Organization for engaging healthcare professionals in the prevention and management of multidrug resistant tuberculosis and cascade trainings in clinical programmatic management of the disease for healthcare professionals.

DOI: 10.1186/s12913-024-10911-6
PMCID: PMC11056065
PMID: 38678263 [Indexed for MEDLINE]

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

32. Lysosomal enzymes and the oxygen burst capability of monocyte-derived macrophages in active drug-resistant tuberculosis patients in relation to cell attachment.

Tuberculosis (Edinb). 2024 May;146:102498. doi: 10.1016/j.tube.2024.102498. Epub 2024 Feb 24.

Iswanti FC(1), Handayani KM(2), Kusumaningrum A(3), Yamazaki T(4), Handayani

D(5), Sadikin M(6).

Author information:
(1)Department of Biochemistry and Molecular Biology, Faculty of Medicine, Universitas Indonesia, 10430, Indonesia; Center of Hypoxia and Oxidative Stress Studies, Indonesia. Electronic address: febriana.iswanti@ui.ac.id.
(2)Master's Programme in Biomedical Sciences, Faculty of Medicine, Universitas Indonesia, 10430, Indonesia; Faculty of Medicine, Universitas Baiturrahmah, 25172, Indonesia. Electronic address: kurnia_maidarmi@fk.unbrah.ac.id.
(3)Department of Microbiology, Faculty of Medicine, Universitas Indonesia, Universitas Indonesia Hospital, 10430, Indonesia. Electronic address: kusumaningrum.ardiana@gmail.com.
(4)Research Center for Macromolecules and Biomaterials, National Institute for Materials Science (NIMS), Tsukuba, 305-0047, Ibaraki, Japan. Electronic address: YAMAZAKI.tomohiko@nims.go.jp.
(5)Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Indonesia, Universitas Indonesia Hospital, 10430, Indonesia. Electronic address: diahzulfitri@yahoo.com.
(6)Department of Biochemistry and Molecular Biology, Faculty of Medicine, Universitas Indonesia, 10430, Indonesia; Center of Hypoxia and Oxidative Stress Studies, Indonesia. Electronic address: sadikinmohamad@gmail.com.

Drug resistance to tuberculosis (TB) has become an obstacle in eliminating tuberculosis. The transmission of drug-resistant TB from patients increases the incidence of primary drug-resistant (DR) TB in individuals who are in close contact. Therefore, it is necessary to incorporate an immunological approach into preventive therapy. This study focuses on the activity of lysosomal enzymes, oxygen bursts, and the attachment ability of macrophages among individuals diagnosed with active drug-resistant TB compared with close contacts with latent TB or healthy cases. We measured macrophage oxygen burst ability (Water-soluble tetrazolium salt (WST) test, Nitric Oxide production, and myeloperoxidase activity) and the degradative ability of lysosomes (activity of the β-glucuronidase and acid phosphatase enzymes). Six active DR-TB patients and 18 close-contact cases (8 Latent Tuberculosis Infection (LTBI); 10 healthy) were recruited at Universitas Indonesia Hospital. The macrophage attachment of the LTBI group was higher than in the other groups. NO production, myeloperoxidase activity, β-glucuronidase, and acid phosphatase were higher in the active DR-TB group. A negative correlation was uncovered between phagocytosis and NO production, myeloperoxidase activity, and lysosomal enzymes. The difference in macrophage function is expected to be a further reference in active DR-TB treatment or preventive therapy.

DOI: 10.1016/j.tube.2024.102498
PMID: 38461765 [Indexed for MEDLINE]

Conflict of interest statement: Declaration of competing interest We have no conflicts of interest to disclose. All authors declare that they have no conflicts of interest.

33. Catastrophic costs incurred by tuberculosis affected households from Thailand's first national tuberculosis patient cost survey.

Sci Rep. 2024 May 16;14(1):11205. doi: 10.1038/s41598-024-56594-1.

Youngkong S(1)(2), Kamolwat P(3), Wongrot P(4), Thavorncharoensap M(5)(6), Chaikledkaew U(5)(6), Nateniyom S(3), Pungrassami P(3), Praditsitthikorn N(7), Mahasirimongkol S(8), Jittikoon J(9), Nishikiori N(10), Baena IG(10), Yamanaka T(10)(11)(12).

Author information:
(1)Mahidol University Health Technology Assessment (MUHTA) Graduate Program, Mahidol University, Bangkok, Thailand. sitaporn.you@mahidol.edu.
(2)Social and Administrative Pharmacy Division, Department of Pharmacy, Faculty of Pharmacy, Mahidol University, Bangkok, Thailand. sitaporn.you@mahidol.edu.
(3)Division of Tuberculosis, Department of Disease Control, Ministry of Public Health, Bangkok, Thailand.
(4)Faculty of Nursing, Mahidol University, Nakhon Pathom, Thailand.
(5)Mahidol University Health Technology Assessment (MUHTA) Graduate Program, Mahidol University, Bangkok, Thailand.
(6)Social and Administrative Pharmacy Division, Department of Pharmacy, Faculty of Pharmacy, Mahidol University, Bangkok, Thailand.
(7)Department of Disease Control, Ministry of Public Health, Nonthaburi, Thailand.
(8)Department of Medical Sciences, Ministry of Public Health, Nonthaburi, Thailand.
(9)Department of Biochemistry, Faculty of Pharmacy, Mahidol University, Bangkok, Thailand.
(10)World Health Organization Global Tuberculosis Programme, Geneva, Switzerland.
(11)Department of Global Health and Development, London School of Hygiene and Tropical Medicine, London, UK.
(12)School of Tropical Medicine and Global Health, Nagasaki University, Nagasaki, Japan.

Tuberculosis (TB) causes an economic impact on the patients and their households. Although Thailand has expanded the national health benefit package for TB treatment, there was no data on out-of-pocket payments and income losses due to TB from patients and their household perspectives. This national TB patient cost survey was conducted to examine the TB-related economic burden, and assess the proportion of TB patients and their households facing catastrophic

total costs because of TB disease. A cross-sectional TB patient cost survey was employed following WHO methods. Structured interviews with a paper-based questionnaire were conducted from October 2019 to July 2021. Both direct and indirect costs incurred from the patient and their household perspective were valued in 2021 and estimated throughout pre- and post-TB diagnosis episodes. We assessed the proportion of TB-affected households facing costs > 20% of household expenditure due to TB. We analyzed 1400 patients including 1382 TB (first-line treatment) and 18 drug-resistant TB patients (DR-TB). The mean total costs per TB episode for all study participants were 903 USD (95% confident interval; CI 771-1034 USD). Of these, total direct non-medical costs were the highest costs (mean, 402 USD, and 95%CI 334-470 USD) incurred per TB-affected household followed by total indirect costs (mean, 393 USD, and 95%CI 315-472 USD) and total direct medical costs (mean, 107 USD, and 95%CI 81-133 USD, respectively. The proportion of TB-affected households facing catastrophic costs was 29.5% (95%CI 25.1-34.0%) for TB (first-line), 61.1% (95%CI 29.6-88.1%) for DR-TB and 29.9% (95%CI 25.6-34.4%) overall. This first national survey highlighted the economic burden on TB-affected households. Travel, food/nutritional supplementation, and indirect costs contribute to a high proportion of catastrophic total costs. These suggest the need to enhance financial and social protection mechanisms to mitigate the financial burden of TB-affected households.

DOI: 10.1038/s41598-024-56594-1
PMCID: PMC11099064
PMID: 38755216 [Indexed for MEDLINE]

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

34. Identification of novel resistance-associated mutations and discrimination within whole-genome sequences of fluoroquinolone-resistant Mycobacterium tuberculosis isolates.

Microbiol Spectr. 2024 Apr 30:e0393023. doi: 10.1128/spectrum.03930-23. Online ahead of print.

Chong Y(1)(2), Li X(1), Long Y(1), Pei S(1), Ren Q(#)(1), Feng F(#)(1), Zhang H(1)(3).

Author information:
(1)Hebei Coordinated Innovation Center of Occupational Health and Safety, School of Public Health, North China University of Science and Technology, Tangshan, Hebei Province, China.
(2)School of Public Health, Shandong Second Medical University, Weifang, Shangdong Province, China.

(3)Keenan Research Centre for Biomedical Science, St. Michael's Hospital, Unity Health Toronto, Toronto, Ontario, Canada.
(#)Contributed equally

This study aims to elucidate additional mutation loci associated with fluoroquinolone (FQ) resistance and evaluate the discriminatory capacity of mutation loci and allele mutation frequencies in identifying FQ-resistant Mycobacterium tuberculosis (MTB) isolates. A random selection of isolates was extracted from an ongoing collection. Drug resistance was determined using the resazurin microtiter assay (REMA) as the gold standard. Mutation loci and the burden of mutations in the quinolone resistance-determining region (QRDR) were elucidated through whole-genome sequencing (WGS). Novel amino acid mutations, namely, G520D and G520T, were identified in the gyrB and associated with FQ resistance. In the context of distinguishing FQ-resistant isolates, the AUC for the QRDR mutation frequency burden (0.969) surpassed that of the mutation locus (0.929), and this difference was statistically significant (P = 0.03). Furthermore, using the resistance mutation locus as a reference, setting the QRDR mutation frequency burden threshold at 1.31% resulted in a 3.60% increase in the accuracy of classifying FQ-resistant isolates (NRI = 3.60%, P < 0.001). The QRDR mutation frequency burden appears to offer superior diagnostic efficacy in discriminating FQ-resistant isolates compared to qualitative detection of mutant loci.IMPORTANCEFluoroquinolone (FQ) drugs are recommended as second-line drugs for the treatment of multidrug-resistant tuberculosis. With the massive use of FQ drugs in the clinical treatment of tuberculosis (TB), there is an increasing rate of drug resistance to FQ drugs. In this study, we identified and demonstrated novel amino acid mutations associated with FQ resistance in Mycobacterium tuberculosis (MTB), and we quantified the mutation sites and identified the quinolone resistance-determining region (QRDR) mutation frequency burden as a novel diagnostic method for FQ resistance. We hope that the results of this study will provide data support and a theoretical basis for the rapid diagnosis of FQ-resistant MTB.

DOI: 10.1128/spectrum.03930-23
PMID: 38687077

35. Sputum culture reversion in longer treatments with bedaquiline, delamanid, and repurposed drugs for drug-resistant tuberculosis.

Nat Commun. 2024 May 9;15(1):3927. doi: 10.1038/s41467-024-48077-8.

Kho S(1), Seung KJ(1)(2), Huerga H(3), Bastard M(3), Khan PY(4)(5), Mitnick CD(1)(2)(6), Rich ML(1)(2), Islam S(7), Zhizhilashvili D(8), Yeghiazaryan L(9), Nikolenko EN(10), Zarli K(11), Adnan S(12), Salahuddin N(12), Ahmed S(13), Vargas ZHR(14), Bekele A(15), Shaimerdenova A(16), Tamirat M(17), Gelin A(18), Vilbrun SC(19), Hewison C(#)(20), Khan U(#)(5), Franke M(#)(21)(22).

Author information:
(1)Division of Global Health Equity, Brigham and Women's Hospital, Boston, MA, USA.
(2)Partners in Health, 800 Boylston Street Suite 300, Boston, MA, USA.
(3)Epicentre, 14-34 Avenue Jean Jaurès, Paris, France.
(4)Department of Clinical Research, London School of Hygiene & Tropical Medicine, London, UK.
(5)Interactive Research and Development Global, Singapore, Singapore.
(6)Department of Global Health and Social Medicine, Harvard Medical School, Boston, MA, USA.
(7)Interactive Research and Development, Dhaka, Bangladesh.
(8)Médecins sans Frontières, Tbilisi, Georgia.
(9)National Center for Pulmonology, Yerevan, Armenia.
(10)Republican Research and Practical Centre for Pulmonology and Tuberculosis, Minsk, Belarus.
(11)Médecins sans Frontières, Yangon, Myanmar.
(12)Indus Hospital and Health Network, Karachi, Pakistan.
(13)Interactive Research and Development, Karachi, Pakistan.
(14)Maria Auxiliadora Hospital, San Juan de Miraflores, Peru.
(15)Department of Internal Medicine, Tikur Anbessa Specialized Hospital and Addis Ababa University, College of Health Sciences, Addis Ababa, Ethiopia.
(16)Karaganda Regional Center of Phthisiopulmonology, Karaganda, Kazakhstan.
(17)Partners in Health, Lesotho, Maseru, Lesotho.
(18)Zanmi Lasante, Port-au-Prince, Haiti.
(19)Haitian Group for the Study of Kaposi's Sarcoma and Opportunistic Infections (GHESKIO), Port-au-Prince, Haiti.
(20)Medical Department, Médecins sans Frontières, Paris, France.
(21)Partners in Health, 800 Boylston Street Suite 300, Boston, MA, USA. molly_franke@hms.harvard.edu.
(22)Department of Global Health and Social Medicine, Harvard Medical School, Boston, MA, USA. molly_franke@hms.harvard.edu.
(#)Contributed equally

Sputum culture reversion after conversion is an indicator of tuberculosis (TB) treatment failure. We analyze data from the endTB multi-country prospective observational cohort (NCT03259269) to estimate the frequency (primary endpoint) among individuals receiving a longer (18-to-20 month) regimen for multidrug- or rifampicin-resistant (MDR/RR) TB who experienced culture conversion. We also conduct Cox proportional hazard regression analyses to identify factors associated with reversion, including comorbidities, previous treatment, cavitary disease at conversion, low body mass index (BMI) at conversion, time to conversion, and number of likely-effective drugs. Of 1,286 patients, 54 (4.2%) experienced reversion, a median of 173 days (97-306) after conversion. Cavitary disease, BMI < 18.5, hepatitis C, prior treatment with second-line drugs, and longer time to initial culture conversion were positively associated with reversion. Reversion was uncommon. Those with cavitary disease, low BMI,

hepatitis C, prior treatment with second-line drugs, and in whom culture conversion is delayed may benefit from close monitoring following conversion.

DOI: 10.1038/s41467-024-48077-8
PMCID: PMC11082252
PMID: 38724531 [Indexed for MEDLINE]

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

36. Prevalence and genetic basis of Mycobacterium tuberculosis resistance to pretomanid in China.

Ann Clin Microbiol Antimicrob. 2024 May 3;23(1):40. doi: 10.1186/s12941-024-00697-0.

Zhao B(#)(1), Zheng H(#)(2), Timm J(#)(3), Song Z(1), Pei S(4), Xing R(1), Guo Y(2), Ma L(5), Li F(2), Li Q(5), Li Y(6), Huang L(6), Teng C(1), Wang N(1), Gupta A(3), Juneja S(3), Huang F(7), Zhao Y(8), Ou X(9).

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, 102206, China.
(2)Laboratory of Respiratory Diseases, Beijing Key Laboratory of Pediatric Respiratory Infection Diseases, Beijing Children's Hospital, Key Laboratory of Major Diseases in Children, Ministry of Education, National Clinical Research Center for Respiratory Diseases, Beijing Pediatric Research Institute, Capital Medical University, National Center for Children's Health, Beijing, 100045, China.
(3)TB Alliance, New York, United States of America.
(4)School of Public Health, Peking University, Beijing, 100191, China.
(5)Institute of Tuberculosis Prevention and Control, Gansu Provincial Center for Disease Control and Prevention, Lanzhou, 730020, China.
(6)Department of Tuberculosis Control, Chengde Center of Disease Prevention and Control, Chengde, 067000, China.
(7)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, 102206, China. huangfei@chinacdc.cn.
(8)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, 102206, China. zhaoyl@chinacdc.cn.
(9)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, 102206, China. ouxc@chinacdc.cn.
(#)Contributed equally

BACKGROUND: Pretomanid is a key component of new regimens for the treatment of drug-resistant tuberculosis (TB) which are being rolled out globally. However, there is limited information on the prevalence of pre-existing resistance to the drug.
METHODS: To investigate pretomanid resistance rates in China and its underlying genetic basis, as well as to generate additional minimum inhibitory concentration (MIC) data for epidemiological cutoff (ECOFF)/breakpoint setting, we performed MIC determinations in the Mycobacterial Growth Indicator Tube™ (MGIT) system, followed by WGS analysis, on 475 Mycobacterium tuberculosis (MTB) isolated from Chinese TB patients between 2013 and 2020.
RESULTS: We observed a pretomanid MIC distribution with a 99% ECOFF equal to 0.5 mg/L. Of the 15 isolates with MIC values > 0.5 mg/L, one (MIC = 1 mg/L) was identified as MTB lineage 1 (L1), a genotype previously reported to be intrinsically less susceptible to pretomanid, two were borderline resistant (MIC = 2-4 mg/L) and the remaining 12 isolates were highly resistant (MIC ≥ 16 mg/L) to the drug. Five resistant isolates did not harbor mutations in the known pretomanid resistant genes.
CONCLUSIONS: Our results further support a breakpoint of 0.5 mg/L for a non-L1 MTB population, which is characteristic of China. Further, our data point to an unexpected high (14/475, 3%) pre-existing pretomanid resistance rate in the country, as well as to the existence of yet-to-be-discovered pretomanid resistance genes.

DOI: 10.1186/s12941-024-00697-0
PMCID: PMC11069242
PMID: 38702782 [Indexed for MEDLINE]

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

37. Effectiveness, cost, and safety of four regimens recommended by WHO for RR/MDR-TB treatment: a cohort study in Eastern China.

Ann Med. 2024 Dec;56(1):2344821. doi: 10.1080/07853890.2024.2344821. Epub 2024 May 2.

Gu P(1), Lu P(2), Ding H(2), Liu Q(2), Ding X(2), Chen Y(1), Zhu L(2).

Author information:
(1)School of International Pharmaceutical Business, China Pharmaceutical

University, Nanjing, China.
(2)Department of Chronic Communicable Disease, Center for Disease Control and Prevention of Jiangsu Province, Nanjing, China.

BACKGROUND: To compare the effectiveness, cost, and safety of four regimens recommended by the World Health Organization (WHO) for rifampicin resistance/multidrug-resistance tuberculosis (RR/MDR-TB) Treatment in Eastern China.
METHODS: We performed a cohort study among patients with RR/MDR between 2020 and 2022 in Jiangsu Province. The treatment success rate, cost, and drug adverse reaction rate were compared.
RESULTS: Between 2020 and 2022, 253 RR/MDR-TB patients were enrolled in the study. 37 (14.62%), 76 (30.04%), 74 (29.25%), and 66 (26.09%) patients had the short-term regimens, the new long-term oral regimens, the new long-term injectable regimens, and the traditional long-term regimens, respectively. The treatment success rate was the highest among patients treated with the short-term regimen (75.68%) and was the lowest among patients treated with the traditional long-term regimens (60.61%). The estimated mean cost per favorable outcome was 142.61 thousand Chinese Yuan (CNY), and the short-term regimens showed the lowest cost in the four regimes (88.51 thousand CNY vs. 174.24 thousand CNY, 144.00 thousand CNY, and 134.98 thousand CNY). Incremental cost-effectiveness ratios of the short-term regimens, the new long-term oral regimen, and the new long-term injectable regimens were -3083.04, 6040.09, and 819.68 CNY compared to the traditional long-term regimens.
CONCLUSIONS: For RR/MDR-TB patients in China who meet the criteria for short-term regimens, the short-term regimens were proven to be the most cost-effective of the four regimens recommended by WHO. For RR/MDR-TB patients in China who don't meet the criteria for short-term regimens, the new long-term injectable regimens are more cost-effective than the remaining two regimens.

Plain Language Summary: This is the first study to evaluate the effectiveness, cost, and safety of four regimens recommended by the WHO for RR/MDR-TB treatment in China.For RR/MDR-TB patients in China who meet the criteria for the short-term regimens, the short-term regimens were proven to be the most cost-effective of the four regimens recommended by WHO.

DOI: 10.1080/07853890.2024.2344821
PMCID: PMC11067554
PMID: 38697138 [Indexed for MEDLINE]

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

38. Economic implications of novel regimens for tuberculosis treatment in three high-burden countries: a modelling analysis.
Lancet Glob Health. 2024 Jun;12(6):e995-e1004. doi:

10.1016/S2214-109X(24)00088-3.

Ryckman TS(1), Schumacher SG(2), Lienhardt C(3), Sweeney S(4), Dowdy DW(5), Mirzayev F(2), Kendall EA(6).

Author information:
(1)Division of Infectious Diseases, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA. Electronic address: tryckma1@jh.edu.
(2)Global TB Programme, WHO, Geneva, Switzerland.
(3)Institut de Recherche pour le Développement, Université de Montpellier, Montpellier, France; Department of Global Health and Development, London School of Hygiene & Tropical Medicine, London, UK.
(4)Department of Global Health and Development, London School of Hygiene & Tropical Medicine, London, UK.
(5)Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA.
(6)Division of Infectious Diseases, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA.

BACKGROUND: With numerous trials investigating novel drug combinations to treat tuberculosis, we aimed to evaluate the extent to which future improvements in tuberculosis treatment regimens could offset potential increases in drug costs.
METHODS: In this modelling analysis, we used an ingredients-based approach to estimate prices at which novel regimens for rifampin-susceptible and rifampin-resistant tuberculosis treatment would be cost-neutral or cost-effective compared with standards of care in India, the Philippines, and South Africa. We modelled regimens meeting targets set in the WHO's 2023 Target Regimen Profiles (TRPs). Our decision-analytical model tracked cohorts of adults initiating rifampin-susceptible or rifampin-resistant tuberculosis treatment, simulating their health outcomes and costs accumulated during and following treatment under standard-of-care and novel regimen scenarios. Price thresholds included short-term cost-neutrality (considering only savings accrued during treatment), medium-term cost-neutrality (additionally considering savings from averted retreatments and secondary cases), and cost-effectiveness (incorporating willingness-to-pay for improved health outcomes).
FINDINGS: Total medium-term costs per person treated using standard-of-care regimens were estimated at US$450 (95% uncertainty interval 310-630) in India, $560 (350-860) in the Philippines, and $730 (530-1090) in South Africa for rifampin-susceptible tuberculosis (current drug costs $46) and $2100 (1590-2810) in India, $2610 (2090-3280) in the Philippines, and $3790 (3090-4630) in South Africa for rifampin-resistant tuberculosis (current drug costs $432). A rifampin-susceptible tuberculosis regimen meeting the optimal targets defined in the TRPs could be cost-neutral in the short term at drug costs of $140 (90-210) per full course in India, $230 (130-380) in the Philippines, and $280 (180-460) in South Africa. For rifampin-resistant tuberculosis, short-term cost-neutral

thresholds were higher with $930 (720-1230) in India, $1180 (980-1430) in the Philippines, and $1480 (1230-1780) in South Africa. Medium-term cost-neutral prices were approximately $50-100 higher than short-term cost-neutral prices for rifampin-susceptible tuberculosis and $250-550 higher for rifampin-resistant tuberculosis. Health system cost-neutral prices that excluded patient-borne costs were 45-70% lower (rifampin-susceptible regimens) and 15-50% lower (rifampin-resistant regimens) than the cost-neutral prices that included patient costs. Cost-effective prices were substantially higher. Shorter duration was the most important driver of medium-term savings with novel regimens, followed by ease of adherence.
INTERPRETATION: Improved tuberculosis regimens, particularly shorter regimens or those that facilitate better adherence, could reduce overall costs, potentially offsetting higher prices.
FUNDING: WHO.

DOI: 10.1016/S2214-109X(24)00088-3
PMID: 38762299 [Indexed for MEDLINE]

Conflict of interest statement: Declaration of interests TSR, CL, DWD, and EAK report funding from WHO. TSR and EAK report funding from the Bill & Melinda Gates Foundation. All other authors declare no competing interests.

39. Particulate matter deposition and its impact on tuberculosis severity: A cross-sectional study in Taipei.

Sci Total Environ. 2024 May 10;924:171534. doi: 10.1016/j.scitotenv.2024.171534. Epub 2024 Mar 6.

Makrufardi F(1), Chuang HC(2), Suk CW(3), Lin YC(4), Rusmawatiningtyas D(5), Murni IK(6), Arguni E(7), Chung KF(8), Bai KJ(9).

Author information:
(1)International Ph.D. Program in Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan; Department of Child Health, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada - Dr. Sardjito Hospital, Yogyakarta, Indonesia. Electronic address: firdianmakruf@gmail.com.
(2)National Heart and Lung Institute, Imperial College London, London, UK; School of Respiratory Therapy, College of Medicine, Taipei Medical University, Taipei, Taiwan; Division of Pulmonary Medicine, Department of Internal Medicine, Shuang Ho Hospital, Taipei Medical University, New Taipei City, Taiwan; Cell Physiology and Molecular Image Research Center, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan; Graduate Institute of Medical Sciences, College of Medicine, Taipei Medical University, Taipei, Taiwan. Electronic

address: chuanghc@tmu.edu.tw.
(3)Division of Pulmonary Medicine, Department of Internal Medicine, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan. Electronic address: 95285@w.tmu.edu.tw.
(4)Department of Civil Engineering, National Central University, Taoyuan City, Taiwan. Electronic address: yclin@ncu.edu.tw.
(5)Department of Child Health, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada - Dr. Sardjito Hospital, Yogyakarta, Indonesia. Electronic address: desy.rusmawatiningtyas@ugm.ac.id.
(6)Department of Child Health, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada - Dr. Sardjito Hospital, Yogyakarta, Indonesia. Electronic address: indah.kartika.m@ugm.ac.id.
(7)Department of Child Health, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada - Dr. Sardjito Hospital, Yogyakarta, Indonesia. Electronic address: eggiarguni@ugm.ac.id.
(8)National Heart and Lung Institute, Imperial College London, London, UK. Electronic address: f.chung@imperial.ac.uk.
(9)School of Respiratory Therapy, College of Medicine, Taipei Medical University, Taipei, Taiwan; Division of Pulmonary Medicine, Department of Internal Medicine, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan. Electronic address: bkj@tmu.edu.tw.

The objective of this study was to examine the association between the lung lobe-deposited dose of inhaled fine particulate matter (PM2.5) and chest X-ray abnormalities in different lung lobes of pulmonary tuberculosis (TB), multidrug-resistant tuberculosis (MDR-TB), and non-tuberculosis mycobacteria infections (NTM). A cross-sectional study was conducted between 2014 and 2022, comprising 1073 patients who were recruited from chest department clinic in a tertial refer hospital in Taipei City, Taiwan. Ambient 1-, 7-, and 30-day PM2.5 exposure and the deposition of PM2.5 in different lung lobes were estimated in each subject. The β coefficient for PM2.5 and deposited PM2.5 in lungs with the outcome variables (pulmonary TB, MDR-TB, and NTM infection) was derived through regression analysis and adjusted for age, gender, BMI, smoking status, and family income. We observed that a 1 μg/m3 increase in ambient PM2.5 was associated with an increase of MDR-TB infections of 0.004 times (95%CI: 0.001-0.007). A 1 μg/m3 increase in 1-day and 7-day PM2.5 deposition in left upper lobe and left lower lobe was associated with an increase in chest X-ray abnormalities of 9.19 % and 1.18 % (95%CI: 0.87-17.51 and 95%CI: 0.08-2.28), and 4.52 % and 5.20 % (95%CI: 0.66-8.38 and 95%CI: 0.51-9.89) in left lung of TB patients, respectively. A 1 μg/m3 increase in 30-day PM2.5 deposition in alveolar region was associated with an increase in percent abnormality of 2.50 % (95%CI: 0.65-4.35) in left upper lobe and 3.33 % (95%CI: 0.65-6.01) in right middle lobe, while in total lung was 0.63 % (95%CI: 0.01-1.27) in right upper lobe and 0.37 % (95%CI, 0.06-0.81) in right lung of MDR-TB patients. Inhaled PM2.5 deposition in lungs was associated with an exacerbation of the radiographic severity of pulmonary TB, particularly in pulmonary MDR-TB patients

in upper and middle lobes. Particulate air pollution may potentially exacerbate the radiographic severity and treatment resistance in individuals with pulmonary TB.

DOI: 10.1016/j.scitotenv.2024.171534
PMID: 38453064 [Indexed for MEDLINE]

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

40. Comparison of targeted next-generation sequencing and the Xpert MTB/RIF assay for detection of Mycobacterium tuberculosis in clinical isolates and sputum specimens.

Microbiol Spectr. 2024 May 2;12(5):e0409823. doi: 10.1128/spectrum.04098-23. Epub 2024 Apr 11.

Zhang H(#)(1), Dai X(#)(1), Hu P(2), Tian L(1), Li C(1), Ding B(1), Yang X(1), He X(1).

Author information:
(1)Beijing Center for Disease Prevention and Control, Beijing, China.
(2)Hunan Chest Hospital, Changsha, Hunan Province, China.
(#)Contributed equally

Targeted next-generation sequencing (tNGS) can be used to perform Mycobacterium tuberculosis (MTB) complex-specific amplification or target capture directly from sputum samples, yielding simultaneous coverage of many genes and DNA regions associated with antimicrobial resistance (AMR). Performance comparisons of tNGS and another molecular testing tool, Xpert MTB/rifampicin (RIF), have been empirical. Here, using a dilution series of a RIF-resistant clinical isolate of MTB, we found that tNGS had a slightly lower limit of bacterial detection (102 CFU/mL) compared with Xpert MTB/RIF (103 CFU/mL) in culture medium. However, the minimum detection limit of the rpoB S450L mutation in this isolate was significantly lower with tNGS (102 CFU/mL) than with Xpert MTB/RIF (106 CFU/mL). Sputum samples collected from 129 suspected pulmonary tuberculosis patients were also prospectively studied with the clinical diagnosis as a reference, revealing that the sensitivity of tNGS (48.6%) was higher than those of culture (46.8%), Xpert MTB/RIF (39.4%), and smear microscopy (34.9%) testing. Notably, AMR analysis of 56 MTB-positive samples as determined by tNGS revealed high mutation frequencies of 96.4%, 35.7%, 26.8%, and 19.6% in the following AMR-associated genes: rrs, rpoB, katG, and pncA, respectively. The findings of this study provide theoretical support for the differential clinical application of tNGS and Xpert MTB/RIF and suggest that tNGS has greater application value in

tuberculosis drug resistance monitoring and prevention.IMPORTANCETargeted next-generation sequencing (tNGS) can be used to perform Mycobacterium tuberculosis (MTB) complex-specific amplification or target capture directly from sputum samples, yielding simultaneous coverage of genes and DNA regions associated with antimicrobial resistance (AMR). Performance comparisons of tNGS and Xpert MTB/rifampicin (RIF) have been empirical. The Xpert MTB/RIF assay is a commercial system that uses the nucleic acid amplification detection method for rapid (2 hours) diagnosis of tuberculosis (TB). The cost of the tNGS and Xpert MTB/RIF assays in this study was similar, at USD 98 and USD 70-104 per sample, respectively, but the time required for tNGS (3 days) was much longer than that required for the Xpert MTB/RIF assay. However, tNGS yielded more accurate results and a larger number of AMR-associated gene mutations, which compensated for the extra time and highlighted the greater application value of tNGS in TB drug resistance monitoring and prevention.

DOI: 10.1128/spectrum.04098-23
PMCID: PMC11064545
PMID: 38602399 [Indexed for MEDLINE]

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

41. Discordant results between Xpert MTB/RIF assay and Bactec MGIT 960 culture system regarding the detection of rifampin-resistant Mycobacterium tuberculosis isolates in Wenzhou, China.

Microbiol Spectr. 2024 May 13:e0385923. doi: 10.1128/spectrum.03859-23. Online ahead of print.

He G(#)(1)(2), Zheng Q(#)(2), Wu J(#)(3), Wu L(#)(4), Geng Z(5), Jiang G(3), Huang H(3), Jiang X(1), Yu X(3).

Author information:
(1)Department of Infectious Diseases, Wenzhou Central Hospital, The Dingli Clinical College of Wenzhou Medical University, The Second Affiliated Hospital of Shanghai University, Wenzhou, China.
(2)Laboratory of Infectious Diseases, Wenzhou Central Hospital, The Dingli Clinical College of Wenzhou Medical University, The Second Affiliated Hospital of Shanghai University, Wenzhou, China.
(3)National Clinical Laboratory on Tuberculosis, Beijing Key Laboratory on Drug-Resistant Tuberculosis, Beijing Chest Hospital, Capital Medical University, Beijing, China.
(4)Department of Clinical Laboratory Medicine, Wenzhou Central Hospital, The Dingli Clinical College of Wenzhou Medical University, The Second Affiliated Hospital of Shanghai University, Wenzhou, China.
(5)Beijing Synchrotron Radiation Facility, Institute of High Energy Physics, Chinese Academy of Sciences, Beijing, China.

(#)Contributed equally

This study aimed to assess the possible causes of discordant results between Xpert MTB/RIF (Xpert) and Bactec MGIT 960 Culture System (MGIT960) regarding rifampicin (RIF) susceptibility in Mycobacterium tuberculosis. Patients with previous RIF-resistant tuberculosis who were admitted to Wenzhou Central Hospital from January 2020 to December 2022 were enrolled. The isolates obtained from these patients were subjected to RIF susceptibility tests using Xpert and MGIT960, and the minimum inhibitory concentration (MIC) of RIF was determined by the MYCOTB MIC plate test. Additionally, molecular docking and molecular dynamics (MD) simulations were performed to evaluate the binding efficacy of rpoB and RIF based on rpoB mutations detected in the isolates with discordant RIF susceptibility results. A total of 28 isolates with discordant RIF susceptibility test results were detected, 15 of them were RIF susceptible with MICs ≤ 0.5 μg/mL. Twelve out of 15 isolates contained borderline RIF resistance-associated mutations [L430P (n = 6), H445N (n = 6)], 1 isolate had D435Y and Q429H double mutation, and the remaining 2 isolates had a silent (Q432Q) mutation. Compared with the affinity of RIF toward the wild type (WT) (-45.83 kcal/mol) by MD, its affinity toward L452P (-55.52 kcal/mol), D435Y (-47.39 kcal/mol), L430P (approximately -69.72 kcal/mol), H445N (-49.53 kcal/mol), and Q429H (-55.67 kcal/mol) increased. Borderline RIF resistance-associated mutations were the main cause for the discordant RIF susceptibility results between Xpert and MGIT960, and the mechanisms of the resistance need further investigated.IMPORTANCEThis study is aimed at assessing discordant results between Xpert MTB/RIF (Xpert) assay and Bactec MGIT 960 Culture System (MGIT960) regarding the detection of rifampicin (RIF)-resistant Mycobacterium tuberculosis isolates in Wenzhou, China. The discordant results of RIF between these two assays were mainly caused by borderline RIF resistance-associated mutations, subsequently by silent mutations of rpoB. Borderline RIF resistance- associated mutations detected in our study were demonstrated to not be affected by the affinity of rpoB and RIF by molecular dynamics, and the mechanism of resistance was needed to be clarified. For the discordant results of RIF by Xpert and MGIT960 that occurred, rpoB DNA sequencing was recommended to investigate its association with resistance to RIF.

DOI: 10.1128/spectrum.03859-23
PMID: 38738892

42. Structure-guided identification and characterization of potent inhibitors targeting PhoP and MtrA to combat mycobacteria.

Comput Struct Biotechnol J. 2024 Apr 3;23:1477-1488. doi: 10.1016/j.csbj.2024.04.005. eCollection 2024 Dec.

Su HL(1), Lai SJ(2)(3), Tsai KC(4)(5), Fung KM(6), Lung TL(7), Hsu HM(7), Wu

YC(7), Liu CH(7), Lai HX(7), Lin JH(8)(9), Tseng TS(7).

Author information:
(1)Department of Emergency Medicine, Ditmanson Medical Foundation Chia-Yi Christian Hospital, Chiayi City 600, Taiwan.
(2)Graduate Institute of Biomedical Sciences, China Medical University, Taichung, Taiwan.
(3)Research Center for Cancer Biology, China Medical University, Taichung, Taiwan.
(4)National Research Institute of Chinese Medicine, Ministry of Health and Welfare, Taipei, Taiwan.
(5)Ph.D. Program in Medical Biotechnology, College of Medical Science and Technology, Taipei Medical University, Taipei, Taiwan.
(6)Biomedical Translation Research Center (BioTReC), Academia Sinica, Taipei 11529, Taiwan.
(7)Institute of Molecular Biology, National Chung Hsing University, Taichung,Taiwan.
(8)Department of Industrial Technology, Ministry of Economic Affairs, Taipei, Taiwan.
(9)Food Industry Research and Development Institute, Hsinchu City, Taiwan.

Mycobacteria are causative agents of tuberculosis (TB), which is a global health concern. Drug-resistant TB strains are rapidly emerging, thereby necessitating the urgent development of new drugs. Two-component signal transduction systems (TCSs) are signaling pathways involved in the regulation of various bacterial behaviors and responses to environmental stimuli. Applying specific inhibitors of TCSs can disrupt bacterial signaling, growth, and virulence, and can help combat drug-resistant TB. We conducted a comprehensive pharmacophore-based inhibitor screening and biochemical and biophysical examinations to identify, characterize, and validate potential inhibitors targeting the response regulators PhoP and MtrA of mycobacteria. The constructed pharmacophore model Phar-PR-n4 identified effective inhibitors of formation of the PhoP-DNA complex: ST132 (IC50 = 29 ± 1.6 μM) and ST166 (IC50 = 18 ± 1.3 μM). ST166 (KD = 18.4 ± 4.3 μM) and ST132 (KD = 14.5 ± 0.1 μM) strongly targeted PhoP in a slow-on, slow-off manner. The inhibitory potency and binding affinity of ST166 and ST132 for MtrAC were comparable to those of PhoP. Structural analyses and molecular dynamics simulations revealed that ST166 and ST132 mainly interact with the α8-helix and C-terminal β-hairpin of PhoP, with functionally essential residue hotspots for structure-based inhibitor optimization. Moreover, ST166 has in vitro antibacterial activity against Macrobacterium marinum. Thus, ST166, with its characteristic 1,2,5,6-tetrathiocane and terminal sulphonic groups, has excellent potential as a candidate for the development of novel antimicrobial agents to combat pathogenic mycobacteria.

DOI: 10.1016/j.csbj.2024.04.005
PMCID: PMC11016868
PMID: 38623562

Conflict of interest statement: There are no conflicts of interest to declare.

43. Genetic diversity of Mycobacterium tuberculosis strains isolated from spiritual holy water site attendees in Northwest Ethiopia. A cross-sectional study.

New Microbes New Infect. 2024 Mar 8;59:101235. doi: 10.1016/j.nmni.2024.101235. eCollection 2024 Jun.

Reta MA(1)(2), Said HM(3), Maningi NE(4), Wubetu GY(5)(6), Agonafir M(7), Fourie PB(1).

Author information:
(1)Department of Medical Microbiology, Faculty of Health Sciences, University of Pretoria, Pretoria, South Africa.
(2)Department of Medical Laboratory Science, College of Health Sciences, Woldia University, Woldia, Ethiopia.
(3)National Institute for Communicable Diseases (NICD), Centre for Tuberculosis, Johannesburg, South Africa.
(4)Department of Microbiology, School of Life Sciences, College of Agriculture, Engineering and Science, University of Kwazulu Natal, Durban, South Africa.
(5)Amhara Public Health Institute (APHI), Bahir Dar, Ethiopia.
(6)Centre for Innovative Drug Development and Therapeutic Trials for Africa (CDT-Africa), College of Health Sciences, Addis Ababa University, Addis Ababa, Ethiopia.
(7)Department of Microbial, Cellular and Molecular Biology, Addis Ababa University, Addis Ababa, Ethiopia.

BACKGROUND: The genetic diversity of Mycobacterium tuberculosis complex (MTBC) strains was characterized among isolates from individuals with pulmonary tuberculosis (PTB) symptoms attended holy water sites (HWSs) in the Amhara region, Ethiopia.
METHODS: A cross-sectional study was done from June 2019 to March 2020 to describe the genetic diversity and drug-resistance profiles of MTBC isolates. Sputum specimens were collected and cultured in the Löwenstein-Jensen culture medium. Line Probe Assay, MTBDRplus VER 2.0, and MTBDRsl VER 2.0 were used to detect first-and second-line anti-TB drug-resistance patterns. A spoligotyping technique was utilized to characterize the genetic diversity. Statistical analysis was performed using STATA 15.
RESULTS: Of 560 PTB-symptomatic participants, 122 (21.8%) were culture-positive cases. Spoligotyping of 116 isolates revealed diverse MTBC sublineages, with four major lineages: Euro-American (EA) (Lineage 4), East-African-Indian (EAI) (Lineage 3), Ethiopian (ETH) (Lineage 7), East Asian (EA) (Lineage 2). The

majority (96.6%) of the isolates were EA (lineage 4) and EAI, with proportions of 54.3% and 42.2%, respectively. A total of 31 spoligotype patterns were identified, 26 of which were documented in the SITVIT2 database. Of these, there were 15 unique spoligotypes, while eleven were grouped with 2-17 isolates. SIT149/T3-ETH (n = 17), SIT26/CAS1-DELHI (n = 16), SIT25/CAS1-DELHI (n = 12), and SIT52/T2 (n = 11) spoligotypes were predominant. A rare spoligotype pattern: SIT41/Turkey and SIT1/Beijing, has also been identified in North Shewa. The overall clustering rate of sub-lineages with known SIT was 76.4%.Of the 122 culture-positive isolates tested, 16.4% were resistant to rifampicin (RIF) and/or isoniazid (INH). Multidrug-resistant TB (MDR-TB) was detected in 12.3% of isolates, five of which were fluoroquinolones (FLQs) resistant. SIT149/T3-ETH and SIT21/CAS1-KILI sublineages showed a higher proportion of drug resistance. CONCLUSIONS: Diverse MTBC spoligotypes were identified, with the T and CAS families and EA (lineage 4) predominating. A high prevalence of drug-resistant TB, with SIT149/T3-ETH and CAS1-KILI sublineages comprising a greater share, was observed. A study with large sample size and a sequencing method with stronger discriminatory power is warranted to understand better the genetic diversity of circulating MTBC in this cohort of study, which would help to adopt targeted interventions.

DOI: 10.1016/j.nmni.2024.101235
PMCID: PMC11000200
PMID: 38590765

Conflict of interest statement: The authors declare that there are no conflicts of interest.

44. Whole-genome sequencing of clinical isolates from tuberculosis patients in India: real-world data indicates a high proportion of pre-XDR cases.

Microbiol Spectr. 2024 May 2;12(5):e0277023. doi: 10.1128/spectrum.02770-23. Epub 2024 Apr 10.

Bhanushali A(1), Atre S(2), Nair P(1), Thandaseery GA(1), Shah S(1), Kuruwa S(1), Zade A(1), Nikam C(3), Gomare M(4), Chatterjee A(1).

Author information:
(1)HaystackAnalytics Pvt. Ltd., IIT Bombay, Mumbai, India.
(2)Dr. D.Y. Patil Medical College Hospital and Research Centre, Pune, India.
(3)Thyrocare Technologies Ltd., Navi Mumbai, India.
(4)BrihanMumbai Municipal Corporation, Mumbai, India.

Treatment decisions for tuberculosis (TB) in the absence of full drug-susceptibility data can result in amplifying resistance and may compromise

treatment outcomes. Genomics of Mycobacterium tuberculosis (M.tb) from clinical samples enables detection of drug resistance to multiple drugs. We performed whole-genome sequencing (WGS) for 600 clinical samples from patients with tuberculosis to identify the drug-resistance profile and mutation spectrum. We documented the reasons reported by clinicians for referral. WGS identified a high proportion (51%) of pre-extensively drug-resistant (pre-XDR) cases followed by multidrug-resistant tuberculosis (MDR-TB) (15.5%). This correlates with the primary reason for referral, as non-response to the first-line treatment (67%) and treatment failure or rifampicin resistance (14%). Multivariate analysis indicated that all young age groups ($P < 0.05$), male gender ($P < 0.05$), and Beijing strain ($P < 0.01$) were significant independent predictors of MDR-TB or MDR-TB+ [pre-extensively drug-resistant tuberculosis (XDR-TB) and XDR-TB]. Ser315Thr (72.5%) in the inhA gene and Ser450Leu in the rpoB gene (65.5%) were the most prevalent mutations, as were resistance-conferring mutations to pyrazinamide (41%) and streptomycin (61.33%). Mutations outside the rifampicin resistance-determining region (RRDR), Ile491Phe and Val170Phe, were seen in 1.3% of cases; disputed mutations in rpoB (Asp435Tyr, His445Asn, His445Leu, and Leu430Pro) were seen in 6% of cases, and mutations to newer drugs such as bedaquiline and linezolid in 1.0% and 7.5% of cases, respectively. This study on clinical samples highlights that there is a high proportion of pre-XDR cases and emerging resistance to newer drugs; ongoing transmission of these strains can cause serious threat to public health; and whole-genome sequencing can effectively identify and support precision medicine for TB.
IMPORTANCE: The current study is based on real-world data on the TB drug-resistance profile by whole-genome sequencing of 600 clinical samples from patients with TB in India. This study indicates the clinicians' reasons for sending samples for WGS, which is for difficult-to-treat cases and/or relapse and treatment failure. The study reports a significant proportion of cases with pre-XDR-TB strains that warrant policy makers' attention. It reflects the current iterative nature of the diagnostic tests under programmatic conditions that leads to delays in appropriate diagnosis and empirical treatment. India had an estimated burden of 2.95 million TB cases in 2020 and 135,000 multidrug-resistant cases. However, WGS profiles of M.tb from India remains disproportionately poorly represented. This study adds a significant body of data on the mutation profiles seen in M.tb isolated from patients with TB in India, mutations outside the RRDR, disputed mutations, and resistance-conferring mutations to newer drugs such as bedaquiline and linezolid.

DOI: 10.1128/spectrum.02770-23
PMCID: PMC11064594
PMID: 38597637 [Indexed for MEDLINE]

Conflict of interest statement: A.C., A.Z., A.B., P.N., G.A.T., S.S., and S.K. are employees of HaystackAnalytics Pvt Ltd., which provides commercial genomics services. Other authors declare no competing interests.

45. Identification of novel single nucleotide variants in the drug resistance mechanism of Mycobacterium tuberculosis isolates by whole-genome analysis.

BMC Genomics. 2024 May 14;25(1):478. doi: 10.1186/s12864-024-10390-3.

Qian W(1), Ma N(1), Zeng X(2), Shi M(3), Wang M(4), Yang Z(5)(6), Tsui SK(7)(8).

Author information:
(1)School of Artificial Intelligence, Hangzhou Dianzi University, Hangzhou, 310018, China.
(2)Agricultural Bioinformatics Key Laboratory of Hubei Province and 3D Genomics Research Centre, College of Informatics, Huazhong Agricultural University, Wuhan, 430070, China.
(3)School of Biomedical Sciences, The Chinese University of Hong Kong, Hong Kong SAR, China.
(4)Stanford Cardiovascular Institute, Stanford University School of Medicine, Stanford, CA, 94305, USA.
(5)School of Artificial Intelligence, Hangzhou Dianzi University, Hangzhou, 310018, China. yangzhiyuan@link.cuhk.edu.hk.
(6)School of Biomedical Sciences, The Chinese University of Hong Kong, Hong Kong SAR, China. yangzhiyuan@link.cuhk.edu.hk.
(7)School of Biomedical Sciences, The Chinese University of Hong Kong, Hong Kong SAR, China. kwtsui@cuhk.edu.hk.
(8)Hong Kong Bioinformatics Centre, The Chinese University of Hong Kong, Hong Kong SAR, China. kwtsui@cuhk.edu.hk.

BACKGROUND: Tuberculosis (TB) represents a major global health challenge. Drug resistance in Mycobacterium tuberculosis (MTB) poses a substantial obstacle to effective TB treatment. Identifying genomic mutations in MTB isolates holds promise for unraveling the underlying mechanisms of drug resistance in this bacterium.
METHODS: In this study, we investigated the roles of single nucleotide variants (SNVs) in MTB isolates resistant to four antibiotics (moxifloxacin, ofloxacin, amikacin, and capreomycin) through whole-genome analysis. We identified the drug-resistance-associated SNVs by comparing the genomes of MTB isolates with reference genomes using the MuMmer4 tool.
RESULTS: We observed a strikingly high proportion (94.2%) of MTB isolates resistant to ofloxacin, underscoring the current prevalence of drug resistance in MTB. An average of 3529 SNVs were detected in a single ofloxacin-resistant isolate, indicating a mutation rate of approximately 0.08% under the selective pressure of ofloxacin exposure. We identified a set of 60 SNVs associated with extensively drug-resistant tuberculosis (XDR-TB), among which 42 SNVs were non-synonymous mutations located in the coding regions of nine key genes (ctpI, desA3, mce1R, moeB1, ndhA, PE_PGRS4, PPE18, rpsA, secF). Protein structure modeling revealed that SNVs of three genes (PE_PGRS4, desA3, secF) are close to the critical catalytic active sites in the three-dimensional structure of the

coding proteins.
CONCLUSION: This comprehensive study elucidates novel resistance mechanisms in MTB against antibiotics, paving the way for future design and development of anti-tuberculosis drugs.

DOI: 10.1186/s12864-024-10390-3
PMCID: PMC11094924
PMID: 38745294 [Indexed for MEDLINE]

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

46. Microfluidics produced ATRA-loaded PLGA NPs reduced tuberculosis burden in alveolar epithelial cells and enabled high delivered dose under simulated human breathing pattern in 3D printed head models.

Eur J Pharm Sci. 2024 May 1;196:106734. doi: 10.1016/j.ejps.2024.106734. Epub 2024 Feb 26.

Bahlool AZ(1), Cavanagh B(2), Sullivan AO(3), MacLoughlin R(4), Keane J(5), Sullivan MPO(5), Cryan SA(6).

Author information:
(1)School of Pharmacy and Biomolecular Sciences, Royal College of Surgeons in Ireland (RCSI), 123 St Stephens Green, Dublin 2, D02 YN77, Dublin, Ireland; Tissue Engineering Research Group, Royal College of Surgeons in Ireland (RCSI), 123 St Stephens Green, Dublin, Ireland; Department of Clinical Medicine, Trinity Translational Medicine Institute, St. James's Hospital, Trinity College Dublin, The University of Dublin, Dublin 8, Ireland.
(2)Cellular and Molecular Imaging Core, Royal College of Surgeons in Ireland RCSI, Dublin 2, Ireland.
(3)Research and Development, Science and Emerging Technologies, Aerogen Ltd, Galway Business Park, Dangan, Galway, Ireland.
(4)School of Pharmacy and Biomolecular Sciences, Royal College of Surgeons in Ireland (RCSI), 123 St Stephens Green, Dublin 2, D02 YN77, Dublin, Ireland; Research and Development, Science and Emerging Technologies, Aerogen Ltd, Galway Business Park, Dangan, Galway, Ireland; School of Pharmacy and Pharmaceutical Sciences, Trinity College, D02 PN40 Dublin, Ireland.
(5)Department of Clinical Medicine, Trinity Translational Medicine Institute, St. James's Hospital, Trinity College Dublin, The University of Dublin, Dublin 8, Ireland.
(6)School of Pharmacy and Biomolecular Sciences, Royal College of Surgeons in Ireland (RCSI), 123 St Stephens Green, Dublin 2, D02 YN77, Dublin, Ireland; Tissue Engineering Research Group, Royal College of Surgeons in Ireland (RCSI), 123 St Stephens Green, Dublin, Ireland; SFI Advanced Materials and

Bioengineering Research (AMBER) Centre, RCSI and Trinity College Dublin, Dublin, Ireland; SFI Centre for Research in Medical Devices (CÚRAM), NUIG & RCSI, Dublin, Ireland. Electronic address: scryan@rcsi.com.

Tuberculosis, caused by Mycobacterium tuberculosis (Mtb), is second only to COVID-19 as the top infectious disease killer worldwide. Multi-drug resistant TB (MDR-TB) may arise because of poor patient adherence to medications due to lengthy treatment duration and side effects. Delivering novel host directed therapies (HDT), like all trans retinoic acid (ATRA) may help to improve drug regimens and reduce the incidence of MDR-TB. Local delivery of ATRA to the site of infection leads to higher bioavailability and reduced systemic side effects. ATRA is poorly soluble in water and has a short half-life in plasma. Therefore, it requires a formulation step before it can be administered in vivo. ATRA loaded PLGA nanoparticles suitable for nebulization were manufactured and optimized using a scalable nanomanufacturing microfluidics (MF) mixing approach (MF-ATRA-PLGA NPs). MF-ATRA-PLGA NPs demonstrated a dose dependent inhibition of Mtb growth in TB-infected A549 alveolar epithelial cell model while preserving cell viability. The MF-ATRA-PLGA NPs were nebulized with the Aerogen Solo vibrating mesh nebulizer, with aerosol droplet size characterized using laser diffraction and the estimated delivered dose was determined. The volume median diameter (VMD) of the MF-ATRA-PLGA NPs was 3.00 ± 0.18 μm. The inhaled dose delivered in adult and paediatric 3D printed head models under a simulated normal adult and paediatric breathing pattern was found to be 47.05 ± 3 % and 20.15 ± 3.46 % respectively. These aerosol characteristics of MF-ATRA-PLGA NPs supports its suitability for delivery to the lungs via inhalation. The data generated on the efficacy of an inhalable, scalable and regulatory friendly ATRA-PLGA NPs formulation provides a foundation on which further pre-clinical testing can be built. Overall, the results of this project are promising for future research into ATRA loaded NPs formulations as inhaled host directed therapies for TB.

DOI: 10.1016/j.ejps.2024.106734
PMID: 38417586

47. Trends of type 2 diabetes with pulmonary tuberculosis patients,2013-2022, and changes after the coronavirus disease 2019 (COVID-19) pandemic.

Tuberculosis (Edinb). 2024 May;146:102499. doi: 10.1016/j.tube.2024.102499. Epub 2024 Feb 27.

Wang Z(1), Zhao S(1), Zhang A(1), Quan B(1), Duan C(1), Liang M(1), Yang J(2).

Author information:
(1)Department of Infectious Diseases, Yijishan Hospital of Wannan Medical

College, Wuhu, Anhui, China.
(2)Department of Infectious Diseases, Yijishan Hospital of Wannan Medical College, Wuhu, Anhui, China. Electronic address: yjhpath@163.com.

BACKGROUND: To describe the trends of Type 2 Diabetes with Pulmonary Tuberculosis (T2DM-TB) patients from 2013 to 2022 and to investigate the impact of COVID-19 lockdown on glycemic control and associated factors in T2DM-TB.
METHODS: In this population-based study of the First Affiliated Yijishan Hospital of Wannan Medical College in China, we described the 10-year trends of patients diagnosed with T2DM-TB. We included patients diagnosed with TB, T2DM-TB and T2DM-TB patients for comparative analysis, aged 15 years or older. Data were missing, and both multidrug-resistant (MDR) TB patients and non-T2DM patients were excluded from our study.
RESULTS: We pooled Type 2 Diabetes (T2DM) and Tuberculosis (TB) data from The First Affiliated Yijishan Hospital of Wannan Medical College in China, gathered between January 1, 2013, and December 31, 2022. The data included 14,227 T2DM patients, 6130 TB patients, and 982 T2DM-TB patients. During the past 10 years, the number of inpatients with TB decreased, while the number of patients with T2DM and T2DM-TB increased year by year. To rule out any influence factors, we analyzed the ratio of the three groups. The ratio of TB/T2DM decreased year by year ($p < 0.05$), while the ratio of TB-T2DM/TB increasing year by year ($p = 0.008$). During the COVID-19 epidemic period, there was no significant change in the ratio of TB-T2DM/T2DM ($p = 0.156$). There was no significant change in the proportion of male patients with TB and TB-T2DM ($p = 0.325$; $p = 0.190$), but the proportion of male patients with T2DM showed an increasing trend ($p < 0.001$). The average age of TB patients over the past 10 years was 54.5 ± 18.4 years and showed an increasing trend year by year ($p < 0.001$). However, there was no significant change in the age of T2DM or TB-T2DM patients ($p = 0.064$; $p = 0.241$). Patients data for the first (2013-2017) and the last (2018-2022) five years were compared. We found that the number of T2DM and TB-T2DM in the last five years was significantly higher than in the first five years, but the number of TB was significantly lower than in the first five years. There is a significant statistical difference in the proportion of TB/T2DM and TB-T2DM/TB, which is similar to the previous results. The average age (56.0 ± 17.6 years) of TB patients in the last five years is significantly higher than in the first five years (53.1 ± 18.9) ($p < 0.001$). The number of male patients with T2DM in the last five years is higher than that in the first five years, with significant difference ($p < 0.001$).
CONCLUSION: The trends of T2DM-TB among hospitalized TB patients have increased significantly over the past 10 years, which may be related to the increase in the number of T2DM cases. The COVID-19 pandemic has been effective in controlling the transmission of TB, but it has been detrimental to the control of T2DM. Male patients with T2DM and elderly TB patients are the key populations for future prevention and control efforts.

DOI: 10.1016/j.tube.2024.102499
PMID: 38442538 [Indexed for MEDLINE]

48. Synergistic effects of sulopenem in combination with cefuroxime or durlobactam against Mycobacterium abscessus.

mBio. 2024 May 14:e0060924. doi: 10.1128/mbio.00609-24. Online ahead of print.

Dousa KM(#)(1)(2), Shin E(#)(1)(2), Kurz SG(3), Plummer M(4), Nantongo M(5)(6), Bethel CR(1), Taracila MA(1)(2), Nguyen DC(7), Kreiswith BN(8), Daley CL(9), Remy KE(2), Holland SM(10), Bonomo RA(1)(2)(11)(12)(13)(14)(15).

Author information:
(1)Louis Stokes Cleveland VA Medical Center, Case Western Reserve University, Cleveland, Ohio, USA.
(2)Department of Medicine, Case Western Reserve University School of Medicine, Cleveland, Ohio, USA.
(3)Department of Medicine, University of Tübingen, Tübingen, Germany.
(4)Yale Center for Molecular Discovery, Yale University, New Haven, Connecticut, USA.
(5)Department of Molecular Biology and Microbiology, Case Western Reserve University School of Medicine, Cleveland, Ohio, USA.
(6)Louis Stokes Cleveland VA Medical Center, Cleveland, Ohio, USA.
(7)Department of Pediatrics, Division of Pediatric Infectious Diseases and Department of Internal Medicine, Division of Infectious Diseases, Rush Medical College, Chicago, Illinois, USA.
(8)Center for Discovery and Innovation, Hackensack Meridian Health, Nutley, New Jersey, USA.
(9)Division of Mycobacterial and Respiratory Infections, National Jewish Health, Denver, Colorado, USA.
(10)Laboratory of Clinical Immunology and Microbiology, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland, USA.
(11)CWRU-Cleveland VAMC Center for Antimicrobial Resistance and Epidemiology (Case VA CARES), Cleveland, Ohio, USA.
(12)Department of Pharmacology, Case Western Reserve University School of Medicine, Cleveland, Ohio, USA.
(13)Department of Biochemistry, Case Western Reserve University School of Medicine, Cleveland, Ohio, USA.
(14)Department of Proteomics and Bioinformatics, Case Western Reserve University School of Medicine, Cleveland, Ohio, USA.
(15)GRECC, Louis Stokes Cleveland Department of Veterans Affairs Medical Center, Cleveland, Ohio, USA.
(#)Contributed equally

Mycobacterium abscessus (Mab) affects patients with immunosuppression or underlying structural lung diseases such as cystic fibrosis (CF). Additionally, Mab poses clinical challenges due to its resistance to multiple antibiotics. Herein, we investigated the synergistic effect of dual β-lactams [sulopenem and cefuroxime (CXM)] or the combination of sulopenem and CXM with β-lactamase inhibitors [BLIs-avibactam (AVI) or durlobactam (DUR)]. The sulopenem-CXM combination yielded low minimum inhibitory concentration (MIC) values for 54 clinical Mab isolates and ATCC19977 (MIC50 and MIC90 ≤0.25 µg/mL). Similar synergistic effects were observed in time-kill studies conducted at concentrations achievable in clinical settings. Sulopenem-CXM outperformed monotherapy, yielding ~1.5 Log10 CFU/mL reduction during 10 days. Addition of BLIs enhanced this antibacterial effect, resulting in an additional reduction of CFUs (~3 Log10 for sulopenem-CXM and AVI and ~4 Log10 for sulopenem-DUR). Exploration of the potential mechanisms of the synergy focused on their interactions with L,D-transpeptidases (Ldts; LdtMab1-LdtMab4), penicillin-binding-protein B (PBP B), and D,D-carboxypeptidase (DDC). Acyl complexes, identified via mass spectrometry analysis, demonstrated the binding of sulopenem with LdtMab2-LdtMab4, DDC, and PBP B and CXM with LdtMab2 and PBP B. Molecular docking and mass spectrometry data suggest the formation of a covalent adduct between sulopenem and LdtMab2 after the nucleophilic attack of the cysteine residue at the β-lactam carbonyl carbon, leading to the cleavage of the β-lactam ring and the establishment of a thioester bond linking the LdtMab2 with sulopenem. In conclusion, we demonstrated the biochemical basis of the synergy of sulopenem-CXM with or without BLIs. These findings potentially broaden the selection of oral therapeutic agents to combat Mab.
IMPORTANCE: Treating infections from Mycobacterium abscessus (Mab), particularly those resistant to common antibiotics like macrolides, is notoriously difficult, akin to a never-ending struggle for healthcare providers. The rate of treatment failure is even higher than that seen with multidrug-resistant tuberculosis. The role of combination β-lactams in inhibiting L,D-transpeptidation, the major peptidoglycan crosslink reaction in Mab, is an area of intense investigation, and clinicians have utilized this approach in the treatment of macrolide-resistant Mab, with reports showing clinical success. In our study, we found that cefuroxime and sulopenem, when used together, display a significant synergistic effect. If this promising result seen in lab settings, translates well into real-world clinical effectiveness, it could revolutionize current treatment methods. This combination could either replace the need for more complex intravenous medications or serve as a "step down" to an oral medication regimen. Such a shift would be much easier for patients to manage, enhancing their comfort and likelihood of sticking to the treatment plan, which could lead to better outcomes in tackling these tough infections. Our research delved into how these drugs inhibit cell wall synthesis, examined time-kill data and binding studies, and provided a scientific basis for the observed synergy in cell-based assays.

DOI: 10.1128/mbio.00609-24

PMID: 38742824

PubMed Non Open Access

49. Multidrug-resistant tuberculosis.

Clin Chim Acta. 2024 May 1;559:119701. doi: 10.1016/j.cca.2024.119701. Online ahead of print.

Wulandari DA(1), Hartati YW(1), Ibrahim AU(2), Pitaloka DAE(3), Irkham(4).

Author information:
(1)Department of Chemistry, Faculty of Mathematics and Natural Sciences, Universitas Padjadjaran, Jl. Raya Bandung-Sumedang Km 21, 45363, Indonesia.
(2)Department of Biomedical Engineering, Near East University, Mersin 10, Nicosia 99010, Turkey; Research Center for Science, Technology and Engineering (BILTEM), Near East University, 99138 Nicosia, TRNC, Mersin 10, Turkey.
(3)Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, Universitas Padjadjaran, Bandung, Indonesia.
(4)Department of Chemistry, Faculty of Mathematics and Natural Sciences, Universitas Padjadjaran, Jl. Raya Bandung-Sumedang Km 21, 45363, Indonesia. Electronic address: irkham@unpad.ac.id.

One of predominant contributors to global mortality is tuberculosis (TB), an infection caused by Mycobacterium tuberculosis (MTB). Inappropriate and ineffectual treatment can lead to the development of drug-resistant TB. One of the most common forms of drug-resistant TB is multidrug-resistant tuberculosis (MDR-TB), caused by mutations in the rpoB and katG genes that lead to resistance to anti-TB drugs, rifampicin (RIF) and isoniazid (INH), respectively. Although culturing remains the gold standard, it is not rapid thereby delaying potential treatment and potentially increasing the incidence of MDR-TB. In contrast, molecular techniques provide a highly sensitive and specific alternative. This review discusses the classification of biomarkers used to detect MDR-TB, some of the commonly used anti-TB drugs, and DNA mutations in MTB that lead to anti-TB resistance. The objective of this review is to increase awareness of the need for rapid and precise detection of MDR-TB cases to decrease morbidity and mortality of this infectious disease worldwide.

DOI: 10.1016/j.cca.2024.119701
PMID: 38697459

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.

50. Drug-induced hypothyroidism in tuberculosis.

Expert Rev Endocrinol Metab. 2024 May;19(3):199-206. doi: 10.1080/17446651.2024.2307525. Epub 2024 Jan 23.

Quiroz-Aldave JE(1), Durand-Vásquez MDC(1), Gamarra-Osorio ER(2), Concepción-Urteaga LA(3), Pecho-Silva S(4)(5), Rodríguez-Hidalgo LA(3), Concepción-Zavaleta MJ(4).

Author information:
(1)Division of Non-communicable diseases, Endocrinology research line, Hospital de Apoyo Chepén, Chepén, Perú.
(2)Division of Endocrinology, Hospital Víctor Lazarte Echegaray, Trujillo, Perú.
(3)Division of Pneumology, Hospital Regional Docente de Trujillo, Trujillo, Perú.
(4)Carrera de Medicina Humana, Universidad Científica del Sur, Lima, Perú.
(5)Division of Pneumology, Hospital Nacional Edgardo Rebagliati Martins, Lima, Perú.

INTRODUCTION: Adverse reactions to tuberculosis treatment can impact patient adherence and prognosis. Hypothyroidism is a frequent adverse reaction caused using ethionamide, prothionamide, and para-aminosalicylic acid and is often underdiagnosed.
AREAS COVERED: We searched Scielo, Scopus, and EMBASE databases, including 67 articles. Antitubercular drug-induced hypothyroidism has a prevalence of 17%. It occurs after 2 to 3 months of treatment and resolves within 4 to 6 weeks after discontinuation. It is postulated to result from the inhibition of thyroperoxidase function, blocking thyroid hormone synthesis. Symptoms are nonspecific, necessitating individualized thyroid-stimulating hormone measurement for detection. Specific guidelines for management are lacking, but initiation of treatment with levothyroxine, as is customary for primary hypothyroidism, is recommended. Discontinuation of antitubercular drugs is discouraged, as it may lead to unfavorable consequences.
EXPERT OPINION: Antitubercular drug-induced hypothyroidism is more common than previously thought, affecting one in six MDR-TB patients. Despite diagnostic and treatment recommendations, implementation is hindered in low-income countries due to the lack of certified laboratories. New drugs for tuberculosis treatment may affect thyroid function, requiring vigilant monitoring for complications, including hypothyroidism.

DOI: 10.1080/17446651.2024.2307525
PMID: 38258451 [Indexed for MEDLINE]

51. Clinical research progress of novel antituberculosis drugs on

multidrug-resistant tuberculosis.

Postgrad Med J. 2024 May 18;100(1184):366-372. doi: 10.1093/postmj/qgad140.

Zhong X(1), Lin A(2), Luo J(1), Li Y(1), Chen J(1), Ning C(1), Cao F(1).

Author information:
(1)Department of Pulmonary and Critical Care Medicine, Red Cross Hospital of Yulin City, Yulin, Guangxi 537000, China.
(2)Department of Cardiothoracic Surgery, Red Cross Hospital of Yulin City, Yulin, Guangxi 537000, China.

Multidrug-resistant tuberculosis (MDR-TB) has become a critical challenge to public health, and the prevention and treatment of MDR-TB are of great significance in reducing the global burden of tuberculosis. How to improve the effectiveness and safety of chemotherapy for MDR-TB is a pressing issue that needs to be addressed in tuberculosis control efforts. This article provides a comprehensive review of the clinical application of new antituberculosis drugs in MDR-TB, aiming to provide a scientific basis for the prevention and treatment strategy of MDR-TB.

DOI: 10.1093/postmj/qgad140
PMID: 38200633 [Indexed for MEDLINE]

52. Xpert MTB/XDR assay: rapid TB drug resistance detection.

Infection. 2024 May 6. doi: 10.1007/s15010-024-02260-7. Online ahead of print.

Sethi S(#)(1), Sharma S(#)(2), Aggarwal AN(3), Dhatwalia SK(2), Rana R(4), Yadav R(2).

Author information:
(1)Department of Medical Microbiology, Postgraduate Institute of Medical Education and Research, Chandigarh, 160012, India. sunilsethi10@hotmail.com.
(2)Department of Medical Microbiology, Postgraduate Institute of Medical Education and Research, Chandigarh, 160012, India.
(3)Pulmonary Medicine, Postgraduate Institute of Medical Education and Research, Chandigarh, India.
(4)State TB Cell, Chandigarh, India.
(#)Contributed equally

PURPOSE: To assess the Xpert MTB/XDR assay's efficiency in promptly detecting resistance to isoniazid, fluoroquinolones, ethionamide, and second-line injectable drugs among tuberculosis (TB) patients.

METHODS: From August 2020 to July 2021, TB suspected patient samples were enrolled at a tertiary care center for our study. We conducted mycobacterial culture, phenotypic DST using proportion method in liquid culture at WHO-recommended concentrations, and the line probe assay (LPA). Simultaneously, the Index test, Xpert MTB/XDR, was performed following the manufacturer's instructions.
RESULTS: Among 360 samples, 107 were excluded due to incomplete information. Resistance to isoniazid, levofloxacin and moxifloxacin was found in 45/251, 21/251 and 20/251 samples, respectively by phenotypic DST. The diagnostic accuracy of Index test, taking phenotypic DST as a reference standard, was 95.8%, 99.04%, and 99.05% for isoniazid, levofloxacin, and moxifloxacin, respectively. The Index test assay demonstrated a specificity of 99.1% for detecting SLID resistance, yielding a diagnostic accuracy of 99.2. Comparing the Index test with LPA revealed a significant enhancement in sensitivity for detecting isoniazid resistance (86.7% vs. 82.2%).
CONCLUSIONS: The Index test exhibited promising outcomes in identifying resistance to isoniazid and fluoroquinolones, surpassing the performance of the LPA. This could be valuable for promptly initiating treatment in cases of drug-resistant tuberculosis.

DOI: 10.1007/s15010-024-02260-7
PMID: 38709461

53. Unlocking InhA: Novel approaches to inhibit Mycobacterium tuberculosis.

Bioorg Chem. 2024 May;146:107250. doi: 10.1016/j.bioorg.2024.107250. Epub 2024 Mar 5.

Wahan SK(1), Bhargava G(1), Chawla V(2), Chawla PA(3).

Author information:
(1)Department of Chemical Sciences, I.K. Gujral Punjab Technical University, Kapurthala, India.
(2)University Institute of Pharmaceutical Sciences and Research, Baba Farid University of Health Sciences, Faridkot, Punjab 151203, India.
(3)University Institute of Pharmaceutical Sciences and Research, Baba Farid University of Health Sciences, Faridkot, Punjab 151203, India. Electronic address: pvchawla@gmail.com.

Multidrug-resistant tuberculosis continues to pose a health security risk and remains a public health emergency. Antimicrobial resistance result from treatment regimens that are both insufficient and incomplete leading to the emergence of multidrug-resistant tuberculosis, extensively drug-resistant tuberculosis and totally drug-resistant tuberculosis. The impact of tuberculosis

on the people suffering from HIV (Human immunodeficiency virus infection) have resulted in the increased research efforts in designing and discovery of novel antitubercular drugs that may result in decreasing treatment duration, minimising the need for multiple drug intake, minimising cytotoxicity and enhancing the mechanism of action of drug. While many drugs are available to treat tuberculosis, a precise and timely cure is still absent. Consequently, further investigation is needed to identify more recent molecular equivalents that have the potential to swiftly remove this disease. Isoniazid (INH), a treatment for tuberculosis (TB), targets the enzyme InhA (mycobacterium enoyl acyl carrier protein reductase), the Mycobacterium tuberculosis enoyl-acyl carrier protein (ACP) reductase, most common INH resistance is circumvented by InhA inhibitors that do not require KatG (catalase-peroxidase) activation, as a result, researchers are trying to work in the area of development of InhA inhibitors which could help in eradicating the era of tuberculosis from the world.

DOI: 10.1016/j.bioorg.2024.107250
PMID: 38460337 [Indexed for MEDLINE]

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

54. Genetic factors associated with acquired phenotypic drug resistance and its compensatory evolution during tuberculosis treatment.

Clin Microbiol Infect. 2024 May;30(5):637-645. doi: 10.1016/j.cmi.2024.01.016. Epub 2024 Jan 28.

Zhang G(1), Sun X(2), Fleming J(3), Ran F(2), Luo J(3), Chen H(3), Ju H(4), Wang Z(4), Zhao H(4), Wang C(4), Zhang F(4), Dai X(5), Yang X(5), Li C(6), Liu Y(6), Wang Y(7), Zhang X(8), Jiang Y(9), Wu Z(8), Bi L(10), Zhang H(11).

Author information:
(1)Key Laboratory of RNA Biology, Institute of Biophysics, Chinese Academy of Sciences, Beijing, China; Tianjin Center for Tuberculosis Control, Tianjin, China; University of Chinese Academy of Sciences, Beijing, China.
(2)Key Laboratory of RNA Biology, Institute of Biophysics, Chinese Academy of Sciences, Beijing, China; University of Chinese Academy of Sciences, Beijing, China.
(3)Key Laboratory of RNA Biology, Institute of Biophysics, Chinese Academy of Sciences, Beijing, China.
(4)Tianjin Center for Tuberculosis Control, Tianjin, China.

(5)Beijing Center for Disease Prevention and Control, Beijing, China.
(6)Biobank of Beijing Chest Hospital, Beijing Tuberculosis and Thoracic Tumour Research Institute/Beijing Chest Hospital, Capital Medical University, Beijing, China.
(7)TB Healthcare Co., Ltd., Foshan, China.
(8)Foshan Fourth People's Hospital, Foshan, China.
(9)Shanghai Municipal Center for Disease Prevention and Control, Beijing, China.
(10)Key Laboratory of RNA Biology, Institute of Biophysics, Chinese Academy of Sciences, Beijing, China; Guangzhou National Laboratory, Guangzhou, China; University of Chinese Academy of Sciences, Beijing, China.
(11)Beijing Center for Disease Prevention and Control, Beijing, China.
Electronic address: hongtaizhang@aliyun.com.

OBJECTIVES: We elucidated the factors, evolution, and compensation of antimicrobial resistance (AMR) in Mycobacterium tuberculosis (MTB) isolates under dual pressure from the intra-host environment and anti-tuberculosis (anti-TB) drugs.
METHODS: This retrospective case-control study included 337 patients with pulmonary tuberculosis from 15 clinics in Tianjin, China, with phenotypic drug susceptibility testing results available for at least two time points between January 1, 2009 and December 31, 2016. Patients in the case group exhibited acquired AMR to isoniazid (INH) or rifampicin (RIF), while those in the control group lacked acquired AMR. The whole-genome sequencing (WGS) was conducted on 149 serial longitudinal MTB isolates from 46 patients who acquired or reversed phenotypic INH/RIF-resistance during treatment. The genetic basis, associated factors, and intra-host evolution of acquired phenotypic INH/RIF-resistance were elucidated using a combined analysis.
RESULTS: Anti-TB interruption duration of ≥30 days showed association with acquired phenotypic INH/RIF resistance (aOR = 2·2, 95% CI, 1·0-5·1) and new rpoB mutations (p = 0·024). The MTB evolution was 1·2 (95% CI, 1·02-1·38) single nucleotide polymorphisms per genome per year under dual pressure from the intra-host environment and anti-TB drugs. AMR-associated mutations occurred before phenotypic AMR appearance in cases with acquired phenotypic INH (10 of 16) and RIF (9 of 22) resistances.
DISCUSSION: Compensatory evolution may promote the fixation of INH/RIF-resistance mutations and affect phenotypic AMR. The TB treatment should be adjusted based on gene sequencing results, especially in persistent culture positivity during treatment, which highlights the clinical importance of WGS in identifying reinfection and AMR acquisition before phenotypic drug susceptibility testing.

DOI: 10.1016/j.cmi.2024.01.016
PMID: 38286176 [Indexed for MEDLINE]

55. Population structure and spatial distribution of Mycobacterium tuberculosis in Ethiopia.

Sci Rep. 2024 May 7;14(1):10455. doi: 10.1038/s41598-024-59435-3.

Getahun M(1), Beyene D(2), Mollalign H(3), Diriba G(3), Tesfaye E(3), Yenew B(3), Taddess M(3), Sinshaw W(3), Ameni G(4)(5).

Author information:
(1)Ethiopian Public Health Institute, P.O. Box 1242, Addis Ababa, Ethiopia. mimishaget@yahoo.com.
(2)Department of Microbial, Cellular and Molecular Biology, Addis Ababa University, Addis Ababa, Ethiopia.
(3)Ethiopian Public Health Institute, P.O. Box 1242, Addis Ababa, Ethiopia.
(4)Aklilu Lemma Institute of Pathobiology, Addis Ababa University, Addis Ababa, Ethiopia.
(5)Department of Veterinary Medicine, College of Agriculture and Veterinary Medicine, United Arab Emirates University, Al Ain, United Arab Emirates.

Ethiopia is one of the countries with a high tuberculosis (TB) burden, yet little is known about the spatial distribution of Mycobacterium tuberculosis (Mtb) lineages. This study identifies the spoligotyping of 1735 archived Mtb isolates from the National Drug Resistance Survey, collected between November 2011 and June 2013, to investigate Mtb population structure and spatial distribution. Spoligotype International Types (SITs) and lineages were retrieved from online databases. The distribution of lineages was evaluated using Fisher's exact test and logistic regression models. The Global Moran's Index and Getis-Ord Gi statistic were utilized to identify hotspot areas. Our results showed that spoligotypes could be interpreted and led to 4 lineages and 283 spoligotype patterns in 91% of the isolates, including 4% of those with multidrug/rifampicin resistance (MDR/RR) TB. The identified Mtb lineages were lineage 1 (1.8%), lineage 3 (25.9%), lineage 4 (70.6%) and lineage 7 (1.6%). The proportion of lineages 3 and 4 varied by regions, with lineage 3 being significantly greater than lineage 4 in reports from Gambella (AOR = 4.37, $P < 0.001$) and Tigray (AOR = 3.44, $P = 0.001$) and lineage 4 being significantly higher in Southern Nations Nationalities and Peoples Region (AOR = 1.97, $P = 0.026$) than lineage 3. Hotspots for lineage 1 were located in eastern Ethiopia, while a lineage 7 hotspot was identified in northern and western Ethiopia. The five prevalent spoligotypes, which were SIT149, SIT53, SIT25, SIT37 and SIT26 account for 42.8% of all isolates under investigation, while SIT149, SIT53 and SIT21 account for 52-57.8% of drug-resistant TB cases. TB and drug resistant TB are mainly caused by lineages 3 and 4, and significant proportions of the prevalent spoligotypes also influence drug-resistant TB and the total TB burden. Regional variations in lineages may result from both local and cross-border spread.

DOI: 10.1038/s41598-024-59435-3
PMCID: PMC11076284
PMID: 38714745 [Indexed for MEDLINE]

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

56. In vitro and ex vivo activity of the fluoroquinolone DC-159a against mycobacteria.

J Antibiot (Tokyo). 2024 May;77(5):306-314. doi: 10.1038/s41429-024-00709-3. Epub 2024 Mar 4.

Imperiale BR(1), Mancino MB(2), Moyano RD(3), de la Barrera S(4), Morcillo NS(2).

Author information:
(1)Institute of Experimental Medicine (IMEX)-CONICET, National Academy of Medicine, Buenos Aires City, Argentina. belen_imperiale@yahoo.com.ar.
(2)Dr. Cetrángolo Hospital, Florida, Buenos Aires Province, Argentina.
(3)IABIMO-CONICET, INTA CiCVyA, Hurlingham, Buenos Aires Province, Argentina.
(4)Institute of Experimental Medicine (IMEX)-CONICET, National Academy of Medicine, Buenos Aires City, Argentina.

Antimicrobial resistance is a global health problem. In 2021, it was estimated almost half a million of multidrug-resistant tuberculosis (MDR-TB) cases. Besides, non-tuberculous mycobacteria (NTM) are highly resistant to several drugs and the emergence of fluoroquinolone (FQ) resistant M. tuberculosis (Mtb) is also a global concern making treatments difficult and with variable outcome. The aim of this study was to evaluate the activity of the FQ, DC-159a, against Mtb and NTM and to explore the cross-resistance with the currently used FQs.A total of 12 pre-extensively drug-resistant (XDR) Mtb, 2 XDR, 36 fully drug susceptible strains and 41 NTM isolates were included to estimate the in vitro activity of DC-159a, moxifloxacin (MOX) and levofloxacin (LX), using minimal inhibitory and bactericidal concentration (MIC and MBC). The activity inside the human macrophages and pulmonary epithelial cells were also determined.DC-159a was active in vitro and ex vivo against mycobacteria. Besides, it was more active than MOX/LX. Moreover, no cross-resistance was evidenced between DC-159a and LX/MOX as DC-159a could inhibit Mtb and MAC strains that were already resistant to LX/MOX.DC-159a could be a possible candidate in new therapeutic regimens for MDR/ XDR-TB and mycobacterioses cases.

DOI: 10.1038/s41429-024-00709-3
PMID: 38438500 [Indexed for MEDLINE]

57. New synergistic benzoquinone scaffolds as inhibitors of mycobacterial cytochrome bc1 complex to treat multi-drug resistant tuberculosis.

Eur J Med Chem. 2024 May 7;272:116479. doi: 10.1016/j.ejmech.2024.116479. Online ahead of print.

Chilamakuru NB(1), Vn AD(2), G VB(3), Pallaprolu N(4), Dande A(4), Nair D(2), Pemmadi RV(5), Reddy Y P(6), Peraman R(7).

Author information:
(1)Research Scholar, Manipal Academy of Higher Education, Manipal, 576104, Karnataka, India; RERDS-CPR, Raghavendra Institute of Pharmaceutical Education and Research Campus, Ananthapuramu, 515721, Andhra Pradesh, India.
(2)ICMR-National Institute for Research in Tuberculosis (NIRT), Chennai, 600031, Tamil Nadu, India.
(3)Department of Pharmaceutical Chemistry, Manipal College of Pharmaceutical Sciences, Manipal Academy of Higher Education, Manipal 576104, Karnataka, India.
(4)Department of Pharmaceutical Analysis, National Institute of Pharmaceutical Education and Research (NIPER), Hajipur 844102, Bihar, India.
(5)RERDS-CPR, Raghavendra Institute of Pharmaceutical Education and Research Campus, Ananthapuramu, 515721, Andhra Pradesh, India; Department of Pharmaceutical Chemistry, A.K.R.G College of Pharmacy, Nallajerla, Andhra Pradesh 534112. Electronic address: drraghuveervarma@gmail.com.
(6)RERDS-CPR, Raghavendra Institute of Pharmaceutical Education and Research Campus, Ananthapuramu, 515721, Andhra Pradesh, India.
(7)RERDS-CPR, Raghavendra Institute of Pharmaceutical Education and Research Campus, Ananthapuramu, 515721, Andhra Pradesh, India; Department of Pharmaceutical Analysis, National Institute of Pharmaceutical Education and Research (NIPER), Hajipur 844102, Bihar, India. Electronic address: drram@niperhajipur.ac.in.

Through a comprehensive molecular docking study, a unique series of naphthoquinones clubbed azetidinone scaffolds was arrived with promising binding affinity to Mycobacterial Cytbc1 complex, a drug target chosen to kill multi-drug resistant Mycobacterium tuberculosis (MDR-Mtb). Five compounds from series-2, 2a, 2c, 2g, 2h, and 2j, showcased significant in vitro anti-tubercular activities against Mtb H37Rv and MDR clinical isolates. Further, synergistic studies of these compounds in combination with INH and RIF revealed a potent bactericidal effect of compound 2a at concentration of 0.39 μg/mL, and remaining (2c, 2g, 2h, and 2j) at 0.78 μg/mL. Exploration into the mechanism study through chemo-stress assay and proteome profiling uncovered the down-regulation of key proteins of electron-transport chain and Cytbc1 inhibition pathway. Metabolomics corroborated these proteome findings, and heightened further understanding of

the underlying mechanism. Notably, in vitro and in vivo animal toxicity studies demonstrated minimal toxicity, thus underscoring the potential of these compounds as promising anti-TB agents in combination with RIF and INH. These active compounds adhered to Lipinski's Rule of Five, indicating the suitability of these compounds for drug development. Particular significance of molecules NQ02, 2a, and 2h, which have been patented (Published 202141033473).

DOI: 10.1016/j.ejmech.2024.116479
PMID: 38733886

Conflict of interest statement: Declaration of competing interest The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. Ramalingam Peraman reports financial support was provided by DST - Science and Engineering Research Board, Government of India. Ramalingam Peraman has patent #202141033473 pending to Ramalingam Peraman. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

58. Applications of Inorganic Nanomaterials against Tuberculosis: A Comprehensive Review.

Curr Drug Deliv. 2024 Apr 30. doi: 10.2174/0115672018295247240426055330. Online ahead of print.

Dastidar DG(1), Roy A(1), Ghosh G(1), Mandal S(2).

Author information:
(1)Department of Pharmaceutics, Guru Nanak Institute of Pharmaceutical Science & Technology, 157/F Nilgunj Road, Panihati, Kolkata-700114, West Bengal, India.
(2)Department of Microbiology, University of Kalyani, Kalyani, West Bengal 741235, India.

Tuberculosis (TB) continues to pose a significant global health threat, with millions of new infections recorded annually. Current treatment strategies, such as Directly Observed Treatment (DOT), face challenges, including patient non-compliance and the emergence of drug-resistant TB strains. In response to these obstacles, innovative approaches utilizing inorganic/metallic nanomaterials have been developed to enhance drug delivery to target alveolar macrophages, where Mycobacterium tuberculosis resides. These nanomaterials have shown effectiveness against various strains of TB, offering benefits such as improved drug efficacy, minimized side effects, and sustained drug release at the infection site. This comprehensive review explores the applications of different metal nanoparticles, metal oxide nanoparticles, and metal-metal oxide

hybrid nanoparticles in the management of TB, including multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains. The synergistic effects of combining inorganic nanoparticles with conventional anti-TB drugs have demonstrated promising results in combating TB infections. Further research and development in this field hold great promise for overcoming the challenges faced in current TB therapy and improving patient outcomes.

DOI: 10.2174/0115672018295247240426055330
PMID: 38693736

59. Evaluation of AAICare®-TB sequence analysis tool for accurate diagnosis of drug-resistant tuberculosis: A comparative study with TB-Profiler and Mykrobe.

Tuberculosis (Edinb). 2024 May 8;147:102515. doi: 10.1016/j.tube.2024.102515. Online ahead of print.

Singhal R(1), Hingane S(2), Bhalla M(3), Sharma A(2), Ferdosh S(2), Tiwari A(2), Jayaswal P(2), Yadav RN(3), Arora J(3), Dewan RK(4), Sharma S(4).

Author information:
(1)Department of Microbiology, National Institute of Tuberculosis and Respiratory Diseases, New Delhi, 110030, India. Electronic address: drritugo@gmail.com.
(2)AarogyaAI® Innovations Pvt. Ltd., No. 677, 1st Floor, Suite 918, 13th Cross, Sector 1, HSR Layout, Bangalore, 560102, Karnataka, India.
(3)Department of Microbiology, National Institute of Tuberculosis and Respiratory Diseases, New Delhi, 110030, India.
(4)National Institute of Tuberculosis and Respiratory Diseases, New Delhi, 110030, India.

A rapid and comprehensive drug susceptibility test is essential for eliminating drug resistant tuberculosis. Next generation sequencing (NGS) based susceptibility testing is being explored as a potential substitute for the conventional phenotypic and genotypic testing methods. However, the adoption of NGS based genotypic susceptibility testing depends on the availability of simple, accurate and efficient analysis tools. This preliminary study aimed to evaluate the performance of a Mycobacterium tuberculosis (Mtb) genome analysis pipeline, AAICare®-TB, for susceptibility prediction, in comparison to two widely used gDST prediction tools, TB-Profiler and Mykrobe. This study was performed in a National Reference Laboratory in India on presumptive drug-resistant tuberculosis (DR-TB) isolates. Whole genome sequences of the 120 cultured isolates were obtained through Illumina sequencing on a MiSeq platform. Raw sequences were simultaneously analysed using the three tools. Susceptibility

prediction reports thus generated, were compared to estimate the total concordance and discordance. WHO mutation catalogue (1st edition, 2021) was used as the reference standard for categorizing the mutations. In this study, AAICare®-TB was able to predict drug resistance status for First Line (Streptomycin, Isoniazid, Rifampicin, Ethambutol and Pyrazinamide) and Second Line drugs (Fluoroquinolones, Second Line Injectables and Ethionamide) in 93 samples along with lineage and hetero-resistance as per the WHO guidelines.

DOI: 10.1016/j.tube.2024.102515
PMID: 38744006

60. Efficacy and Safety of Bufei Jiedu Granules in Treating Multidrug-Resistant Pulmonary Tuberculosis: A Multi-center, Double-Blinded and Randomized Controlled Trial.

Chin J Integr Med. 2024 May 11. doi: 10.1007/s11655-024-3812-7. Online ahead of print.

Zhang SY(1), Qiu L(1), Zhang SX(2), Xiao HP(3), Chu NH(4), Zhang X(5), Zhang HQ(6), Zheng PY(2), Zhang HY(1), Lu ZH(7).

Author information:
(1)Institute of Respiratory Diseases, Longhua Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai, 200032, China.
(2)Clinical Research Center, Shanghai University of Traditional Chinese Medicine, Shanghai, 200032, China.
(3)Department of Tuberculosis, Shanghai Pulmonary Hospital, Tongji University, Shanghai, 200433, China.
(4)Department of Tuberculosis, Beijing Chest Hospital, Capital Medical University, Beijing, 101100, China.
(5)Department of Tuberculosis, the Second Hospital of Nanjing, Nanjing, 210003, China.
(6)Department of Tuberculosis, the First Hospital Affiliated to Xinxiang Medical College, Xinxiang, Henan Province, 453100, China.
(7)Institute of Respiratory Diseases, Longhua Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai, 200032, China. Dr_luzh@shutcm.edu.cn.

OBJECTIVE: To assess the efficacy and safety of Bufei Jiedu (BFJD) ranules as adjuvant therapy for patients with multidrug-resistant pulmonary tuberculosis (MDR-PTB).
METHODS: A large-scale, multi-center, double-blinded, and randomized controlled trial was conducted in 18 sentinel hospitals in China from December 2012 to December 2016. A total of 312 MDR-PTB patients were randomly assigned to BFJD Granules or placebo groups (1:1) using a stratified randomization method, which

both received the long-course chemotherapy regimen for 18 months (6 Am-Lfx-P-Z-Pto, 12 Lfx-P-Z-Pto). Meanwhile, patients in both groups also received BFJD Granules or placebo twice a day for a total of 18 months, respectively. The primary outcome was cure rate. The secondary outcomes included time to sputum-culture conversion, changes in lung cavities and quality of life (QoL) of patients. Adverse reactions were monitored during and after the trial.
RESULTS: A total of 216 cases completed the trial, 111 in the BFJD Granules group and 105 in the placebo group. BFJD Granules, as an adjuvant treatment, increased the cure rate by 13.6% at the end of treatment, compared with the placebo (58.4% vs. 44.8%, P=0.02), and accelerated the median time to sputum-culture conversion (5 months vs. 11 months). The cavity closure rate of the BFJD Granules group (50.6%, 43/85) was higher than that of the placebo group (32.1%, 26/81; P=0.02) in patients who completed the treatment. At the end of the intensive treatment, according to the 36-item Short Form, the BFJD Granules significantly improved physical functioning, general health, and vitality of patients relative to the placebo group (all P<0.01). Overall, the death rates in the two groups were not significantly different; 5.1% (8/156) in the BFJD Granules group and 2.6% (4/156) in the placebo group.
CONCLUSIONS: Supplementing BFJD Granules with the long-course chemotherapy regimen significantly increased the cure rate and cavity closure rates, and rapidly improved QoL of patients with MDR-PTB (Registration No. ChiCTR-TRC-12002850).

DOI: 10.1007/s11655-024-3812-7
PMID: 38733454

61. Synchronization of Mycobacterium life cycle: A possible novel mechanism of antimycobacterial drug resistance evolution and its manipulation.

Life Sci. 2024 Jun 1;346:122632. doi: 10.1016/j.lfs.2024.122632. Epub 2024 Apr 13.

Verma H(1), Chauhan A(1), Kumar A(2), Kumar M(3), Kanchan K(4).

Author information:
(1)Amity Institute of Molecular Medicine and Stem Cell Research, Amity University Uttar Pradesh, Noida 201313, India.
(2)Department of Bio Technology, National Institute of Technology, Raipur, India.
(3)Amity Institute of Genome Engineering, Amity University Uttar Pradesh, Noida 201313, India.
(4)Amity Institute of Molecular Medicine and Stem Cell Research, Amity University Uttar Pradesh, Noida 201313, India. Electronic address:

kkanchan@amity.edu.

Mycobacterium Tuberculosis (Mtb) causing Tuberculosis (TB) is a widespread disease infecting millions of people worldwide. Additionally, emergence of drug resistant tuberculosis is a major challenge and concern in high TB burden countries. Most of the drug resistance in mycobacteria is attributed to developing acquired resistance due to spontaneous mutations or intrinsic resistance mechanisms. In this review, we emphasize on the role of bacterial cell cycle synchronization as one of the intrinsic mechanisms used by the bacteria to cope with stress response and perhaps involved in evolution of its drug resistance. The importance of cell cycle synchronization and its function in drug resistance in cancer cells, malarial and viral pathogens is well understood, but its role in bacterial pathogens has yet to be established. From the extensive literature survey, we could collect information regarding how mycobacteria use synchronization to overcome the stress response. Additionally, it has been observed that most of the microbial pathogens including mycobacteria are responsive to drugs predominantly in their logarithmic phase, while they show resistance to antibiotics when they are in the lag or stationary phase. Therefore, we speculate that Mtb might use this novel strategy wherein they regulate their cell cycle upon antibiotic pressure such that they either enter in their low metabolic phase i.e., either the lag or stationary phase to overcome the antibiotic pressure and function as persister cells. Thus, we propose that manipulating the mycobacterial drug resistance could be possible by fine-tuning its cell cycle.

DOI: 10.1016/j.lfs.2024.122632
PMID: 38615748 [Indexed for MEDLINE]

Conflict of interest statement: Declaration of competing interest There is no conflict of interest among authors.

62. Synthesis and biological evaluation of new naphthalimide-thiourea derivatives as potent antimicrobial agents active against multidrug-resistant Staphylococcus aureus and Mycobacterium tuberculosis.

RSC Med Chem. 2024 Mar 19;15(4):1381-1391. doi: 10.1039/d4md00062e. eCollection 2024 Apr 24.

Rana P(1), Parupalli R(1), Akhir A(2), Saxena D(2), Maitra R(2), Imran M(2), Malik P(2), Mahammad Ghouse S(1), Joshi SV(1), Srikanth D(1), Madhavi YV(1), Dasgupta A(2)(3), Chopra S(2)(3), Nanduri S(1).

Author information:
(1)Department of Chemical Sciences, National Institute of Pharmaceutical

Education and Research (NIPER) Hyderabad Telangana-500037 India nandurisrini92@gmail.com.
(2)Division of Molecular Microbiology and Immunology, CSIR-Central Drug Research Institute Sitapur Road, Sector 10, Janakipuram Extension Lucknow-226031 Uttar Pradesh India skchopra007@gmail.com.
(3)AcSIR: Academy of Scientific and Innovative Research (AcSIR) Ghaziabad 201002 India.

The emergence of antibiotic resistance to S. aureus and M. tuberculosis, particularly MRSA, VRSA, and drug-resistant tuberculosis, poses a serious threat to human health. Towards discovering new antibacterial agents, we designed and synthesized a series of new naphthalimide-thiourea derivatives and evaluated them against a panel of bacterial strains consisting of E. coli, S. aureus, K. pneumoniae, P. aeruginosa, A. baumannii and various mycobacterial pathogens. Compounds 4a, 4l, 4m, 4n, 4q, 9f, 9l, 13a, 13d, 13e, 17a, 17b, 17c, 17d, and 17e demonstrated potent antibacterial activity against S. aureus with MIC 0.03-8 μg mL-1. In addition, these compounds have also exhibited potent inhibition against MDR strains of S. aureus, including VRSA with MICs 0.06-4 μg mL-1. Compounds 4h, 4j, 4l, 4m, 4q, 4r, 9a, 9b, 9c, 9d, 9e, 9g, 9h, 9j, 13f and 17e also exhibited good antimycobacterial activity against M. tuberculosis with MIC 2-64 μg mL-1. The cytotoxicity assay using Vero cells revealed that all the compounds were non-toxic and exhibited a favorable selectivity index (SI >40). Time kill kinetics data indicated that compounds exhibited concentration-dependent killing. Furthermore, in silico studies were performed to decipher the possible mechanism of action. Comprehensively, these results highlight the potential of naphthalimide-thiourea derivatives as promising antibacterial agents.

DOI: 10.1039/d4md00062e
PMCID: PMC11042119
PMID: 38665829

Conflict of interest statement: There are no conflicts to declare.

63. Development of a self-microemulsifying drug delivery system to deliver delamanid via a pressurized metered dose inhaler for treatment of multi-drug resistant pulmonary tuberculosis.

Int J Pharm. 2024 Apr 25;655:124031. doi: 10.1016/j.ijpharm.2024.124031. Epub 2024 Mar 21.

Paliwal H(1), Nakpheng T(2), Kumar Paul P(3), Prem Ananth K(2), Srichana T(4).

Author information:
(1)Drug Delivery System Excellence Center, Department of Pharmaceutical

Technology, Faculty of Pharmaceutical Sciences, Prince of Songkla University, Hat Yai, Songkhla, Thailand; Department of Pharmaceutics, Sanjivani College of Pharmaceutical Education and Research, Kopargaon 423603, Maharashtra, India.
(2)Drug Delivery System Excellence Center, Department of Pharmaceutical Technology, Faculty of Pharmaceutical Sciences, Prince of Songkla University, Hat Yai, Songkhla, Thailand.
(3)Drug Delivery System Excellence Center, Department of Pharmaceutical Technology, Faculty of Pharmaceutical Sciences, Prince of Songkla University, Hat Yai, Songkhla, Thailand; Department of Pharmacy, Gono Bishwabidyalay (University), Dhaka 1344, Bangladesh.
(4)Drug Delivery System Excellence Center, Department of Pharmaceutical Technology, Faculty of Pharmaceutical Sciences, Prince of Songkla University, Hat Yai, Songkhla, Thailand. Electronic address: teerapol.s@psu.ac.th.

Tuberculosis (TB) is a serious health issue that contributes to millions of deaths throughout the world and increases the threat of serious pulmonary infections in patients with respiratory illness. Delamanid is a novel drug approved in 2014 to deal with multi-drug resistant TB (MDR-TB). Despite its high efficiency in TB treatment, delamanid poses delivery challenges due to poor water solubility leading to inadequate absorption upon oral administration. This study involves the development of novel formulation-based pressurized metered dose inhalers (pMDIs) containing self-microemulsifying mixtures of delamanid for efficient delivery to the lungs. To identify the appropriate self-microemulsifying formulations, ternary diagrams were plotted using different combinations of surfactant to co-surfactant ratios (1:1, 2:1, and 3:1). The combinations used Cremophor RH40, Poly Ethylene Glycol 400 (PEG 400), and peppermint oil, and those that showed the maximum microemulsion region and rapid and stable emulsification were selected for further characterization. The diluted self-microemulsifying mixtures underwent evaluation of dose uniformity, droplet size, zeta potential, and transmission electron microscopy. The selected formulations exhibited uniform delivery of the dose throughout the canister life, along with droplet sizes and zeta potentials that ranged from 24.74 to 88.99 nm and - 19.27 to - 10.00 mV, respectively. The aerosol performance of each self-microemulsifying drug delivery system (SMEDDS)-pMDI was assessed using the Next Generation Impactor, which indicated their capability to deliver the drug to the deeper areas of the lungs. In vitro cytotoxicity testing on A549 and NCI-H358 cells revealed no significant signs of toxicity up to a concentration of 1.56 µg/mL. The antimycobacterial activity of the formulations was evaluated against Mycobacterium bovis using flow cytometry analysis, which showed complete inhibition by day 5 with a minimum bactericidal concentration of 0.313 µg/mL. Moreover, the cellular uptake studies showed efficient delivery of the formulations inside macrophage cells, which indicated the potential for intracellular antimycobacterial activity. These findings demonstrated the potential of the Delamanid-SMEDDS-pMDI for efficient pulmonary delivery of delamanid to improve its effectiveness in the treatment of multi-drug resistant pulmonary TB.

DOI: 10.1016/j.ijpharm.2024.124031
PMID: 38521375 [Indexed for MEDLINE]

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

64. Comparison of QTc interval changes in drug-resistant tuberculosis patients on delamanid-containing regimens versus shorter treatment regimens.

Int J Risk Saf Med. 2024 May 3. doi: 10.3233/JRS-230024. Online ahead of print.

Jefman Efendi Marzuki HY(1)(2), Nafrialdi N(3), Sawitri N(4), Sugiri YJ(5), Gusti Agung Ayu Putu Sri Darmayani I(1)(6), Ascobat P(3).

Author information:
(1)Program Pendidikan Dokter Spesialis Farmakologi Klinik, FK UI, Jakarta, Indonesia.
(2)Fakultas Kedokteran Universitas Surabaya, Surabaya, Indonesia.
(3)Departemen Farmakologi dan Terapeutik, FK UI, Jakarta, Indonesia.
(4)Rumah Sakit Paru M. Goenawan Partowidigdo, Gadog Cisarua, Indonesia.
(5)RSUD Dr. Saiful Anwar, Malang, Indonesia.
(6)Badan Pengawas Obat dan Makanan, Jakarta, Indonesia.

BACKGROUND: Delamanid (DLM) is a relatively new drug for drug-resistant tuberculosis (DR-TB) that has been used in Indonesia since 2019 despite its limited safety data. DLM is known to inhibit hERG potassium channel with the potential to cause QT prolongation which eventually leads to Torsades de pointes (TdP).
OBJECTIVE: This study aims to analyse the changes of QTc interval in DR-TB patients on DLM regimen compared to shorter treatment regimens (STR).
METHODS: A retrospective cohort was implemented on secondary data obtained from two participating hospitals. The QTc interval and the changes in QTc interval from baseline (ΔQTc) were assessed every 4 weeks for 24 weeks.
RESULTS: The maximum increased of QTc interval and ΔQTc interval were smaller in the DLM group with mean difference of 18,6 (95%CI 0.3 to 37.5) and 31.6 milliseconds (95%CI 14.1 to 49.1) respectively. The proportion of QTc interval prolongation in DLM group were smaller than STR group (RR=0.62; 95%CI 0.42 to 0.93).
CONCLUSION: This study has shown that DLM regimens are less likely to increase QTc interval compared to STR. However, close monitoring of the risk of QT interval prolongation needs to be carried out upon the use of QT interval

prolonging antituberculoid drugs.

DOI: 10.3233/JRS-230024
PMID: 38701163

65. Effectiveness of preventive treatment among different age groups and Mycobacterium tuberculosis infection status: a systematic review and individual-participant data meta-analysis of contact tracing studies.

Lancet Respir Med. 2024 May 8:S2213-2600(24)00083-3. doi: 10.1016/S2213-2600(24)00083-3. Online ahead of print.

Martinez L(1), Seddon JA(2), Horsburgh CR(3), Lange C(4), Mandalakas AM(5); TB Contact Studies Consortium.

Collaborators: Martinez L, Seddon J, Liu Q, Acuna Villaorduna C, Bonnet M, Carvalho ACC, Chan PC, Hill PC, Lopez-Varela E, Donkor S, Graham SM, Villalba JA, Grandjean L, Zellweger JP, Wang JY, Verhagen LM, van Schalkwykn C, van der Loeff MFS, Sloot R, Trieu L, Ahuja SD, Yoshiyama T, Mazahir R, Martinsonn NA, Jones-López EC, Altet N, Kato S, Fang CT, Geis S, Hauri A, Long R, Doblner CC, Cayla JA, Chakhaia T, Chen C, García-Basteiro AL, Triasih R, Huang LM, Sharma S, Hannoun D, Malone LL, Ling DL, Kritski A, Stein CM, Malik A, Augusto O, Vashishtha R, Boulahbal F, Boom WH, Shen Y, Hesseling AC, Horsburgh CR, Lange C, Mandalakas AM.

Author information:
(1)Boston University School of Public Health, Department of Epidemiology, Boston, MA, USA. Electronic address: leomarti@bu.edu.
(2)Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Stellenbosch University, Stellenbosch, South Africa; Department of Infectious Disease, Imperial College London, London, UK.
(3)Boston University School of Public Health, Department of Epidemiology, Boston, MA, USA.
(4)German Center for Infection Research, Partner Site Hamburg-Lübeck-Borstel-Riems, Borstel, Germany; Global TB and Immigrant Health Program, Baylor College of Medicine and Texas Children's Hospital, Houston, TX, USA; Division of Clinical Infectious Diseases, Research Center Borstel, Borstel, Germany; Respiratory Medicine & International Health, University of Lübeck, Lübeck, Germany.
(5)German Center for Infection Research, Partner Site Hamburg-Lübeck-Borstel-Riems, Borstel, Germany; Global TB and Immigrant Health Program, Baylor College of Medicine and Texas Children's Hospital, Houston, TX, USA; Division of Clinical Infectious Diseases, Research Center Borstel, Borstel, Germany.

BACKGROUND: Tuberculosis is a preventable disease. However, there is debate regarding which individuals would benefit most from tuberculosis preventive treatment and whether these benefits vary in settings with a high burden and low burden of tuberculosis. We aimed to compare the effectiveness of tuberculosis preventive treatment in exposed individuals of differing ages and Mycobacterium tuberculosis infection status while considering tuberculosis burden of the settings.
METHODS: In this systematic review and individual-participant meta-analysis, we investigated the development of incident tuberculosis in people closely exposed to individuals with tuberculosis. We searched for studies published between Jan 1, 1998, and April 6, 2018, in MEDLINE, Web of Science, BIOSIS, and Embase. We restricted our search to cohort studies; case-control studies and outbreak reports were excluded. Two reviewers evaluated titles, abstracts, and full text articles for eligibility. At each stage, two reviewers discussed discrepancies and re-evaluated articles until a consensus was reached. Individual-participant data and a pre-specified list of variables, including characteristics of the exposed contact, the index patient, and environmental characteristics, were requested from authors of all eligible studies; contacts exposed to a drug-resistant tuberculosis index patient were excluded. The primary study outcome was incident tuberculosis. We estimated adjusted hazard ratios (aHRs) for incident tuberculosis with mixed-effects Cox regression models with a study-level random effect. We estimated the number-needed-to-treat (NNT) to prevent one person developing tuberculosis. Propensity score matching procedures were used in all analyses. This study is registered with PROSPERO (CRD42018087022).
FINDINGS: After screening 25 358 records for eligibility, 439 644 participants from 32 cohort studies were included in the individual-participant data meta-analysis. Participants were followed for 1 396 413 person-years (median of 2·7 years [IQR 1·3-4.4]), during which 2496 people were diagnosed with incident tuberculosis. Overall, effectiveness of preventive treatment was 49% (aHR 0·51 [95% CI 0·44-0·60]). Participants with a positive tuberculin-skin-test (TST) or IFNγ release assay (IGRA) result at baseline benefitted from greater protection, regardless of age (0·09 [0·05-0·17] in children younger than 5 years, 0·20 [0·15-0·28] in individuals aged 5-17 years, and 0·17 [0·13-0·22] in adults aged 18 years and older). The effectiveness of preventive treatment was greater in high-burden (0·31 [0·23-0·40]) versus low-burden (0·58 [0·47-0·72]) settings. The NNT ranged from 9 to 34 depending on age among participants with a positive TST or IGRA in both high-burden and low-burden settings; among all contacts (regardless of TST or IGRA test result), the NNT ranged from 29 to 43 in high-burden settings and 213 to 455 in low-burden settings.
INTERPRETATION: Our findings suggest that a risk-targeted strategy prioritising contacts with evidence of M tuberculosis infection might be indicated in low-burden settings, and a broad approach including all contacts should be considered in high-burden settings. Preventive treatment was similarly effective among contacts of all ages.
FUNDING: None.

DOI: 10.1016/S2213-2600(24)00083-3
PMID: 38734022

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

66. Evaluating the biomolecular interaction between delamanid/formulations and human serum albumin by fluorescence, CD spectroscopy and SPR: Effects on protein conformation, kinetic and thermodynamic parameters.

Colloids Surf B Biointerfaces. 2024 May 14;239:113964. doi: 10.1016/j.colsurfb.2024.113964. Online ahead of print.

Tongkanarak K(1), Loupiac C(2), Neiers F(3), Chambin O(4), Srichana T(5).

Author information:
(1)Drug Delivery System Excellence Center, Department of Pharmaceutical Technology, Faculty of Pharmaceutical Sciences, Prince of Songkla University, Hat Yai, Songkhla 90110, Thailand.
(2)Univ. Bourgogne Franche - Comté, L'Institut Agro, Université de Bourgogne, INRAE, UMR PAM 1517, Joint Unit Food Processing and Microbiology, Food and Wine Physico-Chemistry Unit, 1 esplanade Erasme, Dijon 21000, France.
(3)Flavour Perception: Molecular Mechanisms (Flavours), Université de Bourgogne, 7 bd Jeanne d'Arc, Dijon 21000, France.
(4)Univ. Bourgogne Franche - Comté, L'Institut Agro, Université de Bourgogne, INRAE, UMR PAM 1517, Joint Unit Food Processing and Microbiology, Food and Wine Physico-Chemistry Unit, 1 esplanade Erasme, Dijon 21000, France; Department of Pharmaceutical Technology, Faculty of Health Sciences, Université de Bourgogne, 7 bd Jeanne d'Arc, Dijon Cedex 21079, France.
(5)Drug Delivery System Excellence Center, Department of Pharmaceutical Technology, Faculty of Pharmaceutical Sciences, Prince of Songkla University, Hat Yai, Songkhla 90110, Thailand. Electronic address: teerapol.s@psu.ac.th.

Delamanid is an anti-tuberculosis drug used for the treatment of drug-resistant tuberculosis. Since delamanid has a high protein bound potential, even patients with low albumin levels should experience high and rapid delamanid clearance. However, the interaction between delamanid and albumin should be better controlled to optimize drug efficacy. This study was designed to evaluate the binding characteristics of delamanid to human serum albumin (HSA) using various methods: fluorescence spectroscopy, circular dichroism (CD), surface plasmon resonance (SPR), and molecular docking simulation. The fluorescence emission

band without any shift indicated the interaction was not affected by the polarity of the fluorophore microenvironment. The reduction of fluorescence intensity at 344 nm was proportional to the increment of delamanid concentration as a fluorescence quencher. UV-absorbance measurement at the maximum wavelength (λmax, 280 nm) was evaluated using inner filter effect correction. The HSA conformation change was explained by the intermolecular energy transfer between delamanid and HSA during complex formation. The study, which was conducted at temperatures of 298 K, 303 K, and 310 K, revealed a static quenching mechanism that correlated with a decreased of bimolecular quenching rate constant (kq) and binding constant (Ka) at increased temperatures. The Ka was 1.75-3.16 × 104 M-1 with a specific binding site with stoichiometry 1:1. The negative enthalpy change, negative entropy change, and negative Gibbs free energy change demonstrated an exothermic-spontaneous reaction while van der Waals forces and hydrogen bonds played a vital role in the binding. The molecular displacement approach and molecular docking confirmed that the binding occurred mainly in subdomain IIA, which is a hydrophobic pocket of HSA, with a theoretical binding free energy of -9.33 kcal/mol. SPR exhibited a real time negative sensorgram that resulted from deviation of the reflex angle due to ligand delamanid-HSA complex forming. The binding occurred spontaneously after delamanid was presented to the HSA surface. The SPR mathematical fitting model revealed that the association rate constant (kon) was 2.62 × 108 s-1M-1 and the dissociation rate constant (koff) was 5.65 × 10-3 s-1. The complexes were performed with an association constant (KA) of 4.64 × 1010 M-1 and the dissociation constant (KD) of 2.15 × 10-11 M. The binding constant indicated high binding affinity and high stability of the complex in an equilibrium. Modified CD spectra revealed that conformation of the HSA structure was altered by the presence of delamanid during preparation of the proliposomes that led to the reduction of secondary structure stabilization. This was indicated by the percentage decrease of α-helix. These findings are beneficial to understanding delamanid-HSA binding characteristics as well as the drug administration regimen.

DOI: 10.1016/j.colsurfb.2024.113964
PMID: 38761495

Conflict of interest statement: Declaration of Competing Interest There are no conflicts of interest to declare.

67. Confronting Tuberculosis: A Synthetic Quinoline-Isonicotinic Acid Hydrazide Hybrid Compound as a Potent Lead Molecule Against Mycobacterium tuberculosis.

ACS Infect Dis. 2024 May 8. doi: 10.1021/acsinfecdis.4c00277. Online ahead of print.

Vadankula GR(1), Nilkanth VV(1)(2), Rizvi A(1), Yandrapally S(1), Agarwal A(1),

Chirra H(3), Biswas R(3), Arifuddin M(3), Nema V(4), Mallika A(3), Mande SC(5)(2), Banerjee S(1).

Author information:
(1)Laboratory of Molecular Pathogenesis, Department of Biochemistry, School of Life Sciences, University of Hyderabad (UoH), Hyderabad 500046, India.
(2)Bioinformatics Centre, Savitribai Phule Pune University, Pune 411007, India.
(3)Department of Medicinal Chemistry, National Institute of Pharmaceutical Education and Research (NIPER), Hyderabad 500037, India.
(4)Molecular Biology Division, ICMR-National Institute for Translational Virology and AIDS Research, Pune 411026, India.
(5)National Centre for Cell Science, Pune 411007, India.

The current tuberculosis (TB) treatment is challenged by a complex first-line treatment for drug-sensitive (DS) TB. Additionally, the prevalence of multidrug (MDR)- and extensively drug (XDR)-resistant TB necessitates the search for new drug prototypes. We synthesized and screened 30 hybrid compounds containing aminopyridine and 2-chloro-3-formyl quinoline to arrive at a compound with potent antimycobacterial activity, UH-NIP-16. Subsequently, antimycobacterial activity against DS and MDR Mycobacterium tuberculosis (M.tb) strains were performed. It demonstrated an MIC50 value of 1.86 ± 0.21 μM for laboratory pathogenic M.tb strain H37Rv and 3.045 ± 0.813 μM for a clinical M.tb strain CDC1551. UH-NIP-16 also decreased the MIC50 values of streptomycin, isoniazid, ethambutol, and bedaquiline to about 45, 55, 68, and 76%, respectively, when used in combination, potentiating their activities. The molecule was active against a clinical MDR M.tb strain. Cytotoxicity on PBMCs from healthy donors and on human cell lines was found to be negligible. Further, blind docking of UH-NIP-16 using Auto Dock Vina and MGL tools onto diverse M.tb proteins showed high binding affinities with multiple M.tb proteins, the top five targets being metabolically critical proteins CelA1, DevS, MmaA4, lysine acetyltransferase, and immunity factor for tuberculosis necrotizing toxin. These bindings were confirmed by fluorescence spectroscopy using a representative protein, MmaA4. Envisaging that a pathogen will have a lower probability of developing resistance to a hybrid molecule with multiple targets, we propose that UH-NIP-16 can be further developed as a lead molecule with the bacteriostatic potential against M.tb, both alone and in combination with first-line drugs.

DOI: 10.1021/acsinfecdis.4c00277
PMID: 38717380

68. Validation and application of an online extraction and liquid chromatography tandem mass spectrometry assay for the analysis of delamanid and its DM-6705 metabolite in human breast milk.

J Pharm Biomed Anal. 2024 May 16;246:116225. doi: 10.1016/j.jpba.2024.116225. Online ahead of print.

Mkhize B(1), Court R(1), Castel S(1), Joubert A(1), van der Merwe M(1), Maartens G(1), Conradie F(2), Wiesner L(3).

Author information:
(1)Division of Clinical Pharmacology, Department of Medicine, University of Cape Town, Cape Town, South Africa.
(2)Department of Clinical Medicine, University of the Witwatersrand, South Africa.
(3)Division of Clinical Pharmacology, Department of Medicine, University of Cape Town, Cape Town, South Africa. Electronic address: lubbe.wiesner@uct.ac.za.

We developed and validated a bioanalytical assay to quantify delamanid and its key metabolite (DM-6705) in breast milk and aimed to quantify the secretion of these compounds in breast milk. Due to the hydrophobic nature of the analytes, special care was taken during sample preparation to prevent the formation of fatty deposits during protein precipitation. This was followed by online solid phase extraction and liquid chromatography with tandem mass spectrometry for detection. A Restek Viva BiPh C18 column (1.0 mm×50 mm, 5 μm) was used for extraction while chromatographic separation was performed using a Waters Xterra MS C18 (2.1 mm×100 mm, 5 μm) analytical column with an isocratic mobile phase consisting of acetonitrile, methanol, and 5 mM ammonium carbonate. The mass spectrometric detection of the analytes was performed using an AB Sciex 3200 mass spectrometer employing electrospray ionisation in the positive mode with multiple reaction motoring of the relevant precursor and product ions. Delamanid-d4 and OPC-14714 were used as internal standards. A quadratic (weighted 1/x concentration) regression was used to fit calibration curves for delamanid and DM-6705 over the concentration range of 10.0 - 1000 ng/mL. The intra- and inter-day validation accuracies of the quality control samples were between 92.1% and 98.3% for delamanid, and 97.0% and 102.8% for DM-6705. The percentage coefficient of variation (precision) was less than 7.8%. To our knowledge, this is the first report describing the concentrations of delamanid and DM-6705 in the breast milk of patients treated for rifampicin-resistant tuberculosis.

DOI: 10.1016/j.jpba.2024.116225
PMID: 38761519

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.

69. Formulation development, characterization, and evaluation of bedaquiline

fumarate - Soluplus(®) - solid dispersion.

Pharm Dev Technol. 2024 May 10:1-12. doi: 10.1080/10837450.2024.2348585. Online ahead of print.

Pardhi VP(1), Patel M(1), Jain K(1).

Author information:
(1)Department of Pharmaceutics, Drug Delivery and Nanomedicine Research Laboratory, National Institute of Pharmaceutical Education and Research (NIPER), Raebareli, India.

Bedaquiline fumarate (BQF) is classified as a BCS class II drug and has poor water solubility and dissolution rate, which ultimately compromises bioavailability. The objective of this study is to improve the biopharmaceutical properties of BQF through a solid dispersion system by using Soluplus®. Two solid dispersion systems were prepared i.e. binary solid dispersion (BSD) and ternary solid dispersion (TSD) where 14.31-fold and 20.43-fold increase in solubility of BQF was observed with BSD and TSD in comparison to BQF. In our previous research work, we explored the BSD and TSD of BQF with a crystalline polymer, poloxamer 188, which showed an increment in the solubility of BQF. In the current research, amorphous Soluplus® polymer was selected to formulate BSD and TSD with BQF and showed higher solubility than poloxamer 188. The various solid and liquid state characterization results confirmed the presence of an amorphous form of BQF inside solid dispersion. The Fourier transform infrared spectroscopy showed no chemical interactions between BQF and polymer. The cellular uptake results demonstrated higher uptake in Caco-2 cell lines. Pharmacokinetic studies showed enhanced solubility and bioavailability of TSDs. Hence, the present research shows a promising formulation strategy for enhancing the biopharmaceutical performance of BQF by increasing its solubility.

DOI: 10.1080/10837450.2024.2348585
PMID: 38682603

70. Whole-Genome Sequencing Predicting Phenotypic Antitubercular Drug Resistance: Meta-analysis.

J Infect Dis. 2024 May 15;229(5):1481-1492. doi: 10.1093/infdis/jiad480.

Tagami Y(1), Horita N(2), Kaneko M(1), Muraoka S(1), Fukuda N(1), Izawa A(1), Kaneko A(1), Somekawa K(1), Kamimaki C(1), Matsumoto H(1), Tanaka K(1), Murohashi K(1), Aoki A(1), Fujii H(1), Watanabe K(1), Hara Y(1), Kobayashi N(1), Kaneko T(1).

Author information:
(1)Department of Pulmonology, Yokohama City University Graduate School of

Medicine, Yokohama, Japan.
(2)Chemotherapy Center, Yokohama City University Hospital, Yokohama, Japan.

BACKGROUND: For simultaneous prediction of phenotypic drug susceptibility test (pDST) for multiple antituberculosis drugs, the whole genome sequencing (WGS) data can be analyzed using either a catalog-based approach, wherein 1 causative mutation suggests resistance, (eg, World Health Organization catalog) or noncatalog-based approach using complicated algorithm (eg, TB-profiler, machine learning). The aim was to estimate the predictive ability of WGS-based tests with pDST as the reference, and to compare the 2 approaches.
METHODS: Following a systematic literature search, the diagnostic test accuracies for 14 drugs were pooled using a random-effect bivariate model.
RESULTS: Of 779 articles, 44 with 16 821 specimens for meta-analysis and 13 not for meta-analysis were included. The areas under summary receiver operating characteristic curve suggested test accuracy was excellent (0.97-1.00) for 2 drugs (isoniazid 0.975, rifampicin 0.975), very good (0.93-0.97) for 8 drugs (pyrazinamide 0.946, streptomycin 0.952, amikacin 0.968, kanamycin 0.963, capreomycin 0.965, para-aminosalicylic acid 0.959, levofloxacin 0.960, ofloxacin 0.958), and good (0.75-0.93) for 4 drugs (ethambutol 0.926, moxifloxacin 0.896, ethionamide 0.878, prothionamide 0.908). The noncatalog-based and catalog-based approaches had similar ability for all drugs.
CONCLUSIONS: WGS accurately identifies isoniazid and rifampicin resistance. For most drugs, positive WGS results reliably predict pDST positive. The 2 approaches had similar ability.
CLINICAL TRIALS REGISTRATION: UMIN-ID UMIN000049276.

DOI: 10.1093/infdis/jiad480
PMID: 37946558 [Indexed for MEDLINE]

Conflict of interest statement: Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

71. In silico analysis and characterization of potential inhibitors of MmaA3, a methoxy mycolic acid synthase from Mycobacterium tuberculosis.

J Biomol Struct Dyn. 2024 May 10:1-26. doi: 10.1080/07391102.2024.2349545. Online ahead of print.

Chaudhary B(1), Sisodia R(1), Sarmadhikari D(2), Mazumdar PA(3), Asthana S(2), Madhurantakam C(1).

Author information:
(1)Structural and Molecular Biology Laboratory (SMBL), Department of Biotechnology, TERI School of Advanced Studies (TERI SAS), New Delhi, India.
(2)Translational Health Science and Technology Institute (THSTI), NCR Biotech Science Cluster, Faridabad, Haryana, India.
(3)Independent Researcher, New Delhi, India.

The emergence of the multi-and extensively drug-resistant (MDR and XDR) strains of Mycobacterium tuberculosis (M.tb), necessitates paradigm-shifting therapeutic approaches. The impermeable waxy lipid layer, primarily composed of mycolic acids, is a key factor in conferring resistance to conventional drugs. This study introduces a novel strategy to combat drug resistance by targeting Methoxy mycolic acid synthase 3 (MmaA3), a critical enzyme in the mycolic acid biosynthesis pathway. MmaA3 is responsible for the O-methylation of hydroxymycolate precursors and emerges as a promising therapeutic target. Through homology-based modeling, we generated a three-dimensional structure of MmaA3, providing crucial insights into its structural characteristics. High throughput virtual screening was performed against the MmaA3 model, using diverse sources: knowledge-based, FDA-approved Drugbank, and Asinex-Elite libraries. Through rigorous computational analyses, including binding affinity assessments, molecular interactions analysis, and binding free energy calculations, potential inhibitors of MmaA3 have been identified. Subsequent validation studies evaluated the stability of top protein-ligand complexes, and free energy calculations using molecular dynamics simulations. The stability of complexes within the catalytic site was confirmed through RMSD and RMSF profile analyses. Furthermore, binding free energy calculations using the MM-GBSA approach revealed significant binding affinity of identified ligands for MmaA3 target protein, comparable to its substrate/cofactors. These findings underscore the potential of the proposed molecules as candidates for further experimental exploration, offering promising avenues for the development of effective inhibitors against M.tb. Overall, our research contributes to significantly advancing the formulation of progressive therapeutic strategies in combating drug-resistant tuberculosis.Communicated by Ramaswamy H. Sarma.

DOI: 10.1080/07391102.2024.2349545
PMID: 38726567

72. Application of uniportal video-assisted thoracoscopic surgery in the treatment of tuberculous destroyed lung.

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

Zhonghua Wai Ke Za Zhi. 2024 May 1;62(5):432-437. doi: 10.3760/cma.j.cn112139-20230706-00259.

Jiang YH(1), Liu QB(1), Yao L(1), Dai XY(1).

Author information:
(1)Department of Surgery, Wuhan Pulmonary Hospital, Wuhan 430030, China.

Objective: To examine the efficacy of uniportal video-assisted thoracoscopic surgery in the treatment of tuberculous destroyed lung. Methods: This is a retrospective case series study. The clinical data of 33 patients with tuberculous destroyed lung who had received uniportal video-assisted thoracoscopic pulmonary resection from June 2020 to May 2022 in Department of Surgery, Wuhan Pulmonary Hospital were retrospectively analyzed. There were 13 males and 20 females, aged (47.5±16.2) years (range: 19 to 68 years). The course of the disease was from 15 days to 8 years. All 33 cases had pleural adhesions, including 30 cases with total pleural adhesions and atresia. There were 21 cases of calcification of the thoracic lymph node, 17 cases of aspergillus infection, 4 cases of drug-resistant tuberculosis. The surgical incision was located at the midline of the fifth intercostal axilla, length 4 to 5 cm. The principle of separating pleural adhesions was easy first and difficult later, and then appropriate procedures were selected to resect the diseased lung based on the exploration situation. There were 12 cases that underwent superior lobectomy, 11 cases that underwent superior lobectomy and dorsal segmentectomy, 3 cases that underwent inferior lobectomy, 3 cases that underwent pneumonectomy, 2 cases that underwent middle and inferior lobectomy, and 1 case that underwent superior lobectomy, dorsal segmentectomy and basal segment wedgectomy. The surgical techniques, perioperative evaluation and treatment, management of complications, and the outcome were summarized. Results: Six cases were converted to thoracoscope assisted small incision or thoracotomy. For 27 cases who successfully underwent uniportal VATS, the operation time was (238.7±76.8) minutes (range: 60 to 420 minutes), the intraoperative bleeding was (400.4±315.9) ml (range: 50 to 1 200 ml). The duration of postoperative drainage was (12.7±8.3) days (range: 3 to 42 days). The postoperative hospital stay was (15.2±7.9) days (range: 6 to 43 days). Persistent postoperative pulmonary leakage occurred in 12 cases. There were 2 cases of active thoracic bleeding, one of which was cured with conservative treatment. The other case underwent secondary operation. One case of bronchopleural fistula was cured after continuous thoracic drainage to control infection and implantation of one-way bronchial valve through a fiberoptic bronchoscope. Conclusion: For selected patients with tuberculous destroyed lung, choosing the reasonable surgical procedures and techniques, the uniportal VATS could reduce surgical trauma.

Publisher: 目的： 探讨单孔胸腔镜手术治疗结核性毁损肺的临床效果和技术要点。 方法： 本研究为回顾性病例系列研究。回顾性分析2020年6月至2022年5月在武汉市肺科医院外科接受单孔胸腔镜肺切除术的33例结核性毁损肺患者的临床资料。男性13例，女性20例；年龄（47.5±16.2）岁（范围：19~68岁）。所有病例均有胸膜粘连，其中30例全胸膜腔粘连

闭锁，21例有胸腔淋巴结钙化。17例合并曲霉菌感染，4例为耐药结核病。手术切口位于第5肋间腋中线处，长度4~5
cm。术中按照先易后难的原则松解胸膜粘连，根据探查情况选择合适的流程解剖和处理病肺。行上叶切除术12例，上叶切除+下叶背段切除术11例，下叶切除术3例，全肺切除术3例，中叶+下叶切除术2例，上叶切除+下叶背段切除+基底段楔形切除2例。总结分析手术操作技巧、围手术期评估和治疗、并发症处理及治疗效果等。
结果：
6例中转为胸腔镜辅助小切口或开胸手术，其中3例因肺门致密炎性粘连及钙化淋巴结嵌顿，术中损伤肺动脉导致出血而中转为胸腔镜辅助小切口手术；2例因胸腔炎症重，粘连松解后胸壁广泛渗血，中转开胸手术；1例左全肺切除术因纵隔移位、牵拉暴露困难而中转开胸手术。27例顺利完成单孔胸腔镜手术，手术时间（238.7±76.8）min（范围：60~420
min），术中出血量（400.4±315.9）ml（范围：50~1 200 ml），术后引流时间（12.7±8.3）d（范围：3~42
d），术后住院时间（15.2±7.9）d（范围：6~43
d）。术后发生持续性肺漏气12例；胸腔活动性出血2例，1例保守治疗治愈，1例行二次手术止血；支气管胸膜瘘1例持续胸腔引流控制感染后，经纤维支气管镜植入支气管单向活瓣后治愈。
结论：对于严格选择的病例，运用合适的手术流程和技巧，单孔胸腔镜手术的手术结果、早期恢复和远期预后总体较好，可降低手术创伤。.

DOI: 10.3760/cma.j.cn112139-20230706-00259
PMID: 38548613 [Indexed for MEDLINE]

73. 4-(Benzyloxy)phenol-induced p53 exhibits antimycobacterial response triggering phagosome-lysosome fusion through ROS-dependent intracellular Ca(2+) pathway in THP-1 cells.

Microbiol Res. 2024 May;282:127664. doi: 10.1016/j.micres.2024.127664. Epub 2024 Feb 24.

Naik L(1), Patel S(1), Kumar A(1), Ghosh A(2), Mishra A(1), Das M(1), Nayak DK(1), Saha S(2), Mishra A(3), Singh R(4), Behura A(5), Dhiman R(6).

Author information:
(1)Laboratory of Mycobacterial Immunology, Department of Life Science, National Institute of Technology, Rourkela, Odisha 769008, India.

(2)Divison of Bioinformatics, Bose Institute Kolkata, West Bengal 700054, India.
(3)Cellular and Molecular Neurobiology Unit, Indian Institute of Technology Jodhpur, Rajasthan 342011, India.
(4)Tuberculosis Research Laboratory, Translational Health Science and Technology Institute, NCR Biotech Science Cluster, Faridabad-Gurugram Expressway, 3rd Milestone, PO Box # 4, Faridabad, Haryana 121001, India.
(5)Laboratory of Mycobacterial Immunology, Department of Life Science, National Institute of Technology, Rourkela, Odisha 769008, India. Electronic address: ashu.hura@gmail.com.
(6)Laboratory of Mycobacterial Immunology, Department of Life Science, National Institute of Technology, Rourkela, Odisha 769008, India. Electronic address: dhimanr@nitrkl.ac.in.

Drug-resistant tuberculosis (TB) outbreak has emerged as a global public health crisis. Therefore, new and innovative therapeutic options like host-directed therapies (HDTs) through novel modulators are urgently required to overcome the challenges associated with TB. In the present study, we have investigated the anti-mycobacterial effect of 4-(Benzyloxy)phenol. Cell-viability assay asserted that 50 μM of 4-(Benzyloxy)phenol was not cytotoxic to phorbol 12-myristate 13-acetate (PMA) differentiated THP-1 (dTHP-1) cells. It was observed that 4-(Benzyloxy)phenol activates p53 expression by hindering its association with KDM1A. Increased ROS, intracellular Ca2+ and phagosome-lysosome fusion, were also observed upon 4-(Benzyloxy)phenol treatment. 4-(Benzyloxy)phenol mediated killing of intracellular mycobacteria was abrogated in the presence of specific inhibitors of ROS, Ca2+ and phagosome-lysosome fusion like NAC, BAPTA-AM, and W7, respectively. We further demonstrate that 4-(Benzyloxy)phenol mediated enhanced ROS production is mediated by acetylation of p53. Blocking of p53 acetylation by Pifithrin-α (PFT- α) enhanced intracellular mycobacterial growth by blocking the mycobactericidal effect of 4-(Benzyloxy)phenol. Altogether, the results showed that 4-(Benzyloxy)phenol executed its anti-mycobacterial effect by modulating p53-mediated ROS production to regulate phagosome-lysosome fusion through Ca2+ production.

DOI: 10.1016/j.micres.2024.127664
PMID: 38422860 [Indexed for MEDLINE]

Conflict of interest statement: Declaration of Competing Interest The authors state that they do not have any identifiable financial conflicts of interest or personal relationships that might be perceived as exerting an influence on the research presented in this paper.

News Articles

1. WHO updates list of drug-resistant bacteria most threatening to human health

https://www.who.int/news/item/17-05-2024-who-updates-list-of-drug-resistant-bacteria-most-threatening-to-human-health

Earlier this month, the WHO updated their bacterial priority pathogens list and added rifampicin resistant TB as a critical pathogen, the highest priority level. Pathogens are classified by their relative threat to global health and WHO resources are allocated based off the rankings on this list. The last time the BPPL list was updated was in 2017 and TB was not included on the list at that time.

2. Harnessing immune enhancement to combat drug-resistant tuberculosis

https://www.news-medical.net/news/20240426/Harnessing-immune-enhancement-to-combat-drug-resistant-tuberculosis.aspx

Early preclinical testing has shown that precision medicine may aid in treating MDR TB. Researchers recently presented on the implementation of immunotherapy using HDAC inhibitors in conjunction with standard TB regimens. Their early tests showed that several specific HDAC inhibitors reduced bacterial growth in cells by up to 75% without antibiotics. Significant research and clinical testing would still need to be performed to measure a more accurate efficacy.