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

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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.

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

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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.

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3. Drug-Resistant Tuberculosis, Georgia, Kazakhstan, Kyrgyzstan, Moldova, and Ukraine, 2017-2022.

Emerg Infect Dis. 2024 Apr;30(4):831-833. doi: 10.3201/eid3004.231732.

Dahl VN, Butova T, Rosenthal A, Grinev A, Gabrielian A, Vashakidze S, Shubladze N, Toxanbayeva B, Chingissova L, Crudu V, Chesov D, Kalmambetova G, Saparova G, Wejse CM, Butov D; Ukraine TB-Portal Study Group.

In 2021, the World Health Organization recommended new extensively drug-resistant (XDR) and pre-XDR tuberculosis (TB) definitions. In a recent cohort of TB patients in Eastern Europe, we show that XDR TB as currently

defined is associated with exceptionally poor treatment outcomes, considerably worse than for the former definition (31% vs. 54% treatment success).

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4. The clinical profile and outcomes of drug resistant tuberculosis in Central Province of Zambia.

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BACKGROUND: The emergence of Drug Resistant Tuberculosis (DR-TB) is one of the main public health and economic problems facing the world today. DR-TB affects mostly those in economically productive years and prevents them from being part of the workforce needed for economic growth. The aim of this study was to determine the Clinical Profile and Outcomes of DR-TB in Central Province of Zambia.
METHODS: This was a retrospective cross sectional study that involved a review of records of patients with confirmed DR-TB who were managed at Kabwe Central Hospital's Multi-Drug Resistant TB (MDR-TB) Ward from the year 2017 to 2021. 183 patients were managed during this period and all were recruited in the study. Data was collected from DR-TB registers and patient files and then entered in SPSS version 22 where all statistical analyses were performed.
RESULTS: The study revealed that the prevalence of DR-TB among registered TB patients in Central Province was 1.4%. Majority of those affected were adults between the ages of 26 and 45 years (63.9%). The study also found that more than half of the patients were from Kabwe District (60.7%). Other districts with significant number of cases included Kapiri Mposhi 19 (10.4%), Chibombo 12 (6.6%), Chisamba 10 (5.5%), Mumbwa 7 (3.8%) and Mkushi 7 (3.8%). Furthermore, the analysis established that most of the patients had RR-TB (89.6%). 9.3% had MDR-TB, 0.5% had IR-TB and 0.5% had XDR-TB. RR-TB was present in 93.8% of new cases and 88.9% of relapse cases. MDR-TB was present in 6.2% of new cases and 10% of relapse cases. With regard to outcomes of DR-TB, the investigation revealed that 16.9% of the patients had been declared cured, 45.9% had completed treatment, 6% were lost to follow up and 21.3% had died. Risk factors for mortality on multivariate analysis included age 36-45 years (adjusted odds ratio

[aOR] 0.253, 95% CI [0.70-0.908] p = 0.035) and male gender (aOR 0.261, 95% CI [0.107-0.638] p = 0.003).
CONCLUSION: The research has shown beyond doubt that the burden of DR-TB in Central Province is high. The study recommends putting measures in place that will help improve surveillance, early detection, early initiation of treatment and proper follow up of patients.

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5. Compensatory evolution in NusG improves fitness of drug-resistant M. tuberculosis.

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Drug-resistant bacteria are emerging as a global threat, despite frequently being less fit than their drug-susceptible ancestors1-8. Here we sought to define the mechanisms that drive or buffer the fitness cost of rifampicin

resistance (RifR) in the bacterial pathogen Mycobacterium tuberculosis (Mtb). Rifampicin inhibits RNA polymerase (RNAP) and is a cornerstone of modern short-course tuberculosis therapy9,10. However, RifR Mtb accounts for one-quarter of all deaths due to drug-resistant bacteria11,12. We took a comparative functional genomics approach to define processes that are differentially vulnerable to CRISPR interference (CRISPRi) inhibition in RifR Mtb. Among other hits, we found that the universally conserved transcription factor NusG is crucial for the fitness of RifR Mtb. In contrast to its role in Escherichia coli, Mtb NusG has an essential RNAP pro-pausing function mediated by distinct contacts with RNAP and the DNA13. We find this pro-pausing NusG-RNAP interface to be under positive selection in clinical RifR Mtb isolates. Mutations in the NusG-RNAP interface reduce pro-pausing activity and increase fitness of RifR Mtb. Collectively, these results define excessive RNAP pausing as a molecular mechanism that drives the fitness cost of RifR in Mtb, identify a new mechanism of compensation to overcome this cost, suggest rational approaches to exacerbate the fitness cost, and, more broadly, could inform new therapeutic approaches to develop drug combinations to slow the evolution of RifR in Mtb.

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6. Mathematical models of drug-resistant tuberculosis lack bacterial heterogeneity: A systematic review.

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Drug-resistant tuberculosis (DR-TB) threatens progress in the control of TB. Mathematical models are increasingly being used to guide public health decisions on managing both antimicrobial resistance (AMR) and TB. It is important to consider bacterial heterogeneity in models as it can have consequences for predictions of resistance prevalence, which may affect decision-making. We conducted a systematic review of published mathematical models to determine the modelling landscape and to explore methods for including bacterial heterogeneity. Our first objective was to identify and analyse the general characteristics of mathematical models of DR-mycobacteria, including M. tuberculosis. The second objective was to analyse methods of including bacterial heterogeneity in these models. We had different definitions of heterogeneity depending on the model level. For between-host models of mycobacterium, heterogeneity was defined as any model where bacteria of the same resistance level were further differentiated. For bacterial population models, heterogeneity was defined as having multiple distinct resistant populations. The search was conducted following PRISMA guidelines in five databases, with studies included if they were mechanistic or simulation models of DR-mycobacteria. We identified 195 studies modelling DR-mycobacteria, with most being dynamic transmission models of non-treatment intervention impact in M. tuberculosis (n = 58). Studies were set in a limited number of specific countries, and 44% of models (n = 85) included only a single level of "multidrug-resistance (MDR)". Only 23 models (8 between-host) included any bacterial heterogeneity. Most of these also captured multiple antibiotic-resistant classes (n = 17), but six models included heterogeneity in bacterial populations resistant to a single antibiotic. Heterogeneity was usually represented by different fitness values for bacteria resistant to the same antibiotic (61%, n = 14). A large and growing body of mathematical models of DR-mycobacterium is being used to explore intervention impact to support policy as well as theoretical explorations of resistance dynamics. However, the majority lack bacterial heterogeneity, suggesting that important evolutionary effects may be missed.

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

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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.

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

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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.

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

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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.

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10. Ethambutol and meropenem/clavulanate synergy promotes enhanced extracellular and intracellular killing of Mycobacterium tuberculosis.

Antimicrob Agents Chemother. 2024 Apr 3;68(4):e0158623. doi: 10.1128/aac.01586-23. Epub 2024 Feb 27.

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Increasing evidence supports the repositioning of beta-lactams for tuberculosis (TB) therapy, but further research on their interaction with conventional anti-TB agents is still warranted. Moreover, the complex cell envelope of Mycobacterium tuberculosis (Mtb) may pose an additional obstacle to beta-lactam diffusion. In this context, we aimed to identify synergies between beta-lactams and anti-TB drugs ethambutol (EMB) and isoniazid (INH) by assessing antimicrobial effects, intracellular activity, and immune responses. Checkerboard assays with H37Rv and eight clinical isolates, including four drug-resistant strains, exposed that only treatments containing EMB and beta-lactams achieved synergistic effects. Meanwhile, the standard EMB and INH association failed to produce any synergy. In Mtb-infected THP-1 macrophages, combinations of EMB with increasing meropenem (MEM) concentrations consistently displayed superior killing activities over the individual antibiotics. Flow cytometry with BODIPY FL vancomycin, which binds directly to the peptidoglycan (PG), confirmed an increased exposure of this layer after co-treatment. This was reinforced by the high IL-1β secretion levels found in infected macrophages after incubation with MEM concentrations above 5 mg/L, indicating an exposure of the host innate response sensors to pathogen-associated molecular patterns in the PG. Our findings show that the proposed impaired access of beta-lactams to periplasmic transpeptidases is counteracted by concomitant administration with EMB. The efficiency of this combination may be attributed to the synchronized

inhibition of arabinogalactan and PG synthesis, two key cell wall components. Given that beta-lactams exhibit a time-dependent bactericidal activity, a more effective pathogen recognition and killing prompted by this association may be highly beneficial to optimize TB regimens containing carbapenems.IMPORTANCEAddressing drug-resistant tuberculosis with existing therapies is challenging and the treatment success rate is lower when compared to drug-susceptible infection. This study demonstrates that pairing beta-lactams with ethambutol (EMB) significantly improves their efficacy against Mycobacterium tuberculosis (Mtb). The presence of EMB enhances beta-lactam access through the cell wall, which may translate into a prolonged contact between the drug and its targets at a concentration that effectively kills the pathogen. Importantly, we showed that the effects of the EMB and meropenem (MEM)/clavulanate combination were maintained intracellularly. These results are of high significance considering that the time above the minimum inhibitory concentration is the main determinant of beta-lactam efficacy. Moreover, a correlation was established between incubation with higher MEM concentrations during macrophage infection and increased IL-1β secretion. This finding unveils a previously overlooked aspect of carbapenem repurposing against tuberculosis, as certain Mtb strains suppress the secretion of this key pro-inflammatory cytokine to evade host surveillance.

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11. Cost-consequence analysis of ambulatory clinic- and home-based multidrug-resistant tuberculosis management models in Eswatini.

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BACKGROUND: We compared the cost-consequence of a home-based multidrug-resistant

tuberculosis (MDR-TB) model of care, based on task-shifting of directly observed therapy (DOT) and MDR-TB injection administration to lay health workers, to a routine clinic-based strategy within an established national TB programme in Eswatini.
METHODS: Data on costs and effects of the two ambulatory models of MDR-TB care was collected using documentary data and interviews in the Lubombo and Shiselweni regions of Eswatini. Health system, patient and caregiver costs were assessed in 2014 in US$ using standard methods. Cost-consequence was calculated as the cost per patient successfully treated.
RESULTS: In the clinic-based and home-based models of care, respectively, a total of 96 and 106 MDR-TB patients were enrolled in 2014, with treatment success rates of 67.8% and 82.1%. Health system costs per patient treated were slightly lower in the home-based strategy (US$19 598) compared to the clinic-based model (US$20 007). The largest costs in both models were for inpatient care, administration of DOT and injectable treatment, and drugs. Costs incurred by patients and caregivers were considerably higher in the clinic-based model of care due to the higher direct travel costs to the nearest clinic to receive DOT and injections daily. In total, MDR patients in the clinic-based strategy incurred average costs of US$670 compared to US$275 for MDR-TB patients in the home-based model. MDR-TB patients in the home-based programme, where DOT and injections was provided in their homes, only incurred out-of-pocket travel expenses for monthly outpatient treatment monitoring visits averaging US$100. The cost per successfully treated patient was US$31 106 and US$24 157 in the clinic-based and home-based models of care, respectively. The analysis showed that, in addition to the health benefits, direct and indirect costs for patients and their caregivers were lower in the home-based care model.
CONCLUSION: The home-based strategy used less resources and generated substantial health and economic benefits, particularly for patients and their caregivers, and decision makers can consider this approach as an alternative to expand and optimise MDR-TB control in resource-limited settings. Further research to understand the appropriate mix of treatment support components that are most important for optimal clinical and public health outcomes in the ambulatory home-based model of MDR-TB care is necessary.

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interests exist.

12. The recent rapid expansion of multidrug resistant Ural lineage Mycobacterium tuberculosis in Moldova.

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The projected trajectory of multidrug resistant tuberculosis (MDR-TB) epidemics depends on the reproductive fitness of circulating strains of MDR M. tuberculosis (Mtb). Previous efforts to characterize the fitness of MDR Mtb have found that Mtb strains of the Beijing sublineage (Lineage 2.2.1) may be more prone to develop resistance and retain fitness in the presence of resistance-conferring mutations than other lineages. Using Mtb genome sequences from all culture-positive cases collected over two years in Moldova, we estimate the fitness of Ural (Lineage 4.2) and Beijing strains, the two lineages in which MDR is concentrated in the country. We estimate that the fitness of MDR Ural strains substantially exceeds that of other susceptible and MDR strains, and we identify several mutations specific to these MDR Ural strains. Our findings suggest that MDR Ural Mtb has been transmitting efficiently in Moldova and poses a substantial risk of spreading further in the region.

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13. 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.

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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.

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PMID: 38617837

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14. Trends and risk factors for drug-resistant tuberculosis among children in Sichuan, China: A 10-year retrospective analysis, 2013-2022.

Medicine (Baltimore). 2024 Apr 12;103(15):e37643. doi: 10.1097/MD.0000000000037643.

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To investigate the status of the drug-resistant tuberculosis (DR-TB) among children in Sichuan, and to find out the risk factors and high-risk population related to drug resistance among children. The clinical data of tuberculosis patients ≤14 years old with culture-confirmed tuberculosis hospitalized in Chengdu Public Health Clinical Center from January 2013 through December 2022 were collected. Clinical data such as gender, age, ethnicity, history of anti-TB treatment, history of exposure to tuberculosis, nutritional status, and specific drug resistance of the children were collected and recorded. The drug resistance of children in different age groups (0-4 years old, 5-9 years old, 10-14 years old) and different periods (2013-2017 and 2018-2022) were grouped and compared. Logistic regression analysis was to analyze analysis of risk factors of drug resistance in children. A total of 438 children with culture-confirmed tuberculosis were screened. Among them, 26.19% (11/42) were 0 to 4 years old,

33.33% (22/66) were 5 to 9 years old, and 36.67% (121/330) were 10 to 14 years old among the resistant children. There was no statistically significant difference in the resistance rate among the 3 groups (P = .385). The proportions of DR-TB, monoresistant tuberculosis, polydrug-resistant tuberculosis were decreased during 2019 to 2022 compared with 2013 to 2017 (P < .0001). The resistance rates of drug resistant, monoresistant, polydrug-resistant, isoniazid-resistant, and rifampicin resistant during 2018 to 2022 were decreased compared with those from 2013 to 2017 (P < .05), but the multi-drug resistance rate was not decreased (P = .131, without statistical difference). The results of logistic regression analysis showed that male gender OR = 1.566 (95% CI 1.035-2.369), a history of antituberculosis therapy OR = 4.049 (95% CI 1.442-11.367), and pulmonary and extrapulmonary tuberculosis OR = 7.335 (95% CI 1.401-38.392) were risk factors for the development of drug resistance; but fever OR = 0.581 (95% CI 0.355-0.950) was Protective factor. The total drug resistance rate of children in Sichuan showed a downward trend, but the rate of multi-drug-resistant tuberculosis was still at a high level, and the form of drug resistance was still severe. Absence of fever, male, retreatment, and pulmonary concurrent with extrapulmonary tuberculosis are risk factors for DR-TB in children.

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PMID: 38608104 [Indexed for MEDLINE]

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

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

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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.

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16. 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.

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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.

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

Antimicrob Agents Chemother. 2024 Apr 10:e0158323. doi: 10.1128/aac.01583-23. Online ahead of print.

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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.

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PMID: 38597667

18. Triple combination dry powder formulation of pretomanid, moxifloxacin, and pyrazinamide for treatment of multidrug-resistant tuberculosis.

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Both latent and multidrug-resistant tuberculosis (TB) have been causing significant concern worldwide. A novel drug, pretomanid (PA-824), has shown a potent bactericidal effect against both active and latent forms of Mycobacterium tuberculosis (MTb) and a synergistic effect when combined with pyrazinamide and moxifloxacin. This study aimed to develop triple combination spray dried inhalable formulations composed of antitubercular drugs, pretomanid, moxifloxacin, and pyrazinamide (1:2:8 w/w/w), alone (PaMP) and in combination with an aerosolization enhancer, L-leucine (20 % w/w, PaMPL). The formulation PaMPL consisted of hollow, spherical, dimpled particles (<5 μm) and showed good aerosolization behaviour with a fine particle fraction of 70 %. Solid-state characterization of formulations with and without L-leucine confirmed the amorphous nature of moxifloxacin and pretomanid and the crystalline nature of pyrazinamide with polymorphic transformation after the spray drying process. Further, the X-ray photoelectron spectroscopic analysis revealed the predominant surface composition of L-leucine on PaMPL dry powder particles. The dose-response cytotoxicity results showed pyrazinamide and moxifloxacin were non-toxic in both A549 and Calu-3 cell lines up to 150 μg/mL. However, the cell viability gradually decreased to 50 % when the pretomanid concentration increased to 150 μg/mL. The in vitro efficacy studies demonstrated that the triple combination formulation had more prominent antibacterial activity with a minimum inhibitory concentration (MIC) of 1 μg/mL against the MTb H37Rv strain as compared to individual drugs. In conclusion, the triple combination of pretomanid, moxifloxacin, and pyrazinamide as an inhalable dry powder formulation will potentially improve treatment efficacy with fewer systemic side effects in patients suffering from latent and multidrug-resistant TB.

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19. Synergistic combination of antimicrobial peptide and isoniazid as inhalable dry powder formulation against multi-drug resistant tuberculosis.

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Multidrug-resistant tuberculosis (MDR-TB) has posed a serious threat to global public health, and antimicrobial peptides (AMPs) have emerged to be promising candidates to tackle this deadly infectious disease. Previous study has suggested that two AMPs, namely D-LAK120-A and D-LAK120-HP13, can potentiate the effect of isoniazid (INH) against mycobacteria. In this study, the strategy of combining INH and D-LAK peptide as a dry powder formulation for inhalation was explored. The antibacterial effect of INH and D-LAK combination was first evaluated on three MDR clinical isolates of Mycobacteria tuberculosis (Mtb). The minimum inhibitory concentrations (MICs) and fractional inhibitory concentration indexes (FICIs) were determined. The combination was synergistic against Mtb with FICIs ranged from 0.25 to 0.38. The INH and D-LAK peptide at 2:1 mole ratio (equivalent to 1: 10 mass ratio) was identified to be optimal. This ratio was adopted for the preparation of dry powder formulation for pulmonary delivery, with mannitol used as bulking excipient. Spherical particles with mass median aerodynamic diameter (MMAD) of around 5 μm were produced by spray drying. The aerosol performance of the spray dried powder was moderate, as evaluated by the Next Generation Impactor (NGI), with emitted fraction and fine particle fraction

of above 70 % and 45 %, respectively. The circular dichroism spectra revealed that both D-LAK peptides retained their secondary structure after spray drying, and the antibacterial effect of the combination against the MDR Mtb clinical isolates was successfully preserved. The combination was found to be effective against MDR Mtb isolates with KatG or InhA mutations. Overall, the synergistic combination of INH with D-LAK peptide formulated as inhaled dry powder offers a new therapeutic approach against MDR-TB.

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20. A systematic review and meta-analysis of circulating serum and plasma microRNAs in TB diagnosis.

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BACKGROUND: Tuberculosis (TB) ranks as the second leading cause of death globally among all infectious diseases. This problem is likely due to the lack

of biomarkers to differentiate the heterogeneous spectrum of infection. Therefore, the first step in solving this problem is to identify biomarkers to distinguish the different disease states of an individual and treat them accordingly. Circulating microRNA (miRNA) biomarkers are promising candidates for various diseases. In fact, we are yet to conceptualize how miRNA expression influences and predicts TB disease outcomes. Thus, this systematic review and meta-analysis aimed to assess the diagnostic efficacy of circulating miRNAs in Latent TB (LTB) and Active Pulmonary TB (PTB).
METHODS: Literature published between 2012 and 2021 was retrieved from PubMed, Web of Science, Cochrane, Scopus, Embase, and Google Scholar. Articles were screened based on inclusion and exclusion criteria, and their quality was assessed using the QUADAS-2 tool. Funnel plots and forest plots were generated to assess the likelihood of study bias and heterogeneity, respectively.
RESULTS: After the screening process, seven articles were selected for qualitative analysis. The study groups, which consisted of Healthy Control (HC) vs. TB and LTB vs. TB, exhibited an overall sensitivity of 81.9% (95% CI: 74.2, 87.7) and specificity of 68.3% (95% CI: 57.8, 77.2), respectively. However, our meta-analysis results highlighted two potentially valuable miRNA candidates, miR-197 and miR-144, for discriminating TB from HC. The miRNA signature model (miR197-3p, miR-let-7e-5p, and miR-223-3p) has also been shown to diagnose DR-TB with a sensitivity of 100%, but with a compromised specificity of only 75%.
CONCLUSION: miRNA biomarkers show a promising future for TB diagnostics. Further multicentre studies without biases are required to identify clinically valid biomarkers for different states of the TB disease spectrum.
SYSTEMATIC REVIEW REGISTRATION: PROSPERO (CRD42022302729).

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21. Perspectives on development and advancement of new tuberculosis vaccines.

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Tuberculosis (TB) remains a leading cause of death worldwide and is estimated to have caused 1.3 million deaths worldwide in 2022. Approximately one quarter of the world's population are infected with Mycobacterium tuberculosis, of whom up to 10% will progress to developing active TB disease. Achieving the World Health Organization End TB Strategy targets of a 95% reduction in TB mortality and a 90% reduction in TB incidence worldwide by 2035 remains a daunting task. The continuing spread of multidrug-resistant TB adds another obstacle to achieving global TB control. Larger funding pledges coupled with technological advances have recently enabled the enhancement of TB vaccine development efforts. These are yielding a pipeline of over 17 products currently in different stages of clinical trials. Emerging promising phase I and II trial results and advancement to phase III trials have necessitated "vaccine preparedness" in parallel so that a smooth transition from any positive clinical trial result to phase IV evaluation and implementation into policy and practice can follow. Promotion of

a human rights-based approach, which recognizes and upholds the fundamental rights of all affected by the disease, is essential to ensure universal access to quality TB vaccines, regardless of their background or personal circumstances.

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Conflict of interest statement: Declarations of competing interest All authors have an academic interest in TB. The authors have no competing interest to declare. The views expressed by the authors are their own and do not reflect those of their individual institutions.

22. Performance of the BD MAX MDR-TB assay in a clinical setting and its impact on the clinical course of patients with pulmonary tuberculosis: a retrospective before-after study.

J Yeungnam Med Sci. 2024 Apr 5. doi: 10.12701/jyms.2024.00024. Online ahead of print.

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BACKGROUND: Missing isoniazid (INH) resistance during tuberculosis (TB) diagnosis can worsen the outcomes of INH-resistant TB. The BD MAX MDR-TB assay (BD MAX) facilitates the rapid detection of TB and INH and rifampin (RIF) resistance; however, data related to its performance in clinical setting remain limited. Moreover, its effect on treatment outcomes has not yet been studied.
METHODS: We compared the performance of BD MAX for the detection of INH/RIF resistances to that of the line probe assay (LPA) in patients with pulmonary TB (PTB), using the results of a phenotypic drug sensitivity test as a reference standard. The treatment outcomes of patients who used BD MAX were compared with those of patients who did not.
RESULTS: Of the 83 patients included in the study, the BD MAX was used for an initial PTB diagnosis in 39 patients. The sensitivity of BD MAX for detecting PTB was 79.5%. The sensitivity and specificity of BD MAX for INH resistance were

both 100%, whereas these were 50.0% and 95.8%, respectively, for RIF resistance. The sensitivity and specificity of BD MAX were comparable to those of LPA. The BD MAX group had a shorter time interval from specimen request to the initiation of anti-TB drugs (2.0 days vs. 5.5 days, p=0.001).
CONCLUSION: BD MAX showed comparable performance to conventional tests for detecting PTB and INH/RIF resistances. The implementation of BD MAX as a diagnostic tool for PTB resulted in a shorter turnaround time for the initiation of PTB treatment.

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23. Development of a multiplex droplet digital PCR method for detection and monitoring of Mycobacterium tuberculosis and drug-resistant tuberculosis.

Ann Clin Microbiol Antimicrob. 2024 Apr 5;23(1):29. doi: 10.1186/s12941-024-00687-2.

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BACKGROUND: The prevalence of multidrug-resistant tuberculosis (MDR-TB) among Korean tuberculosis patients is about 4.1%, which is higher than the OECD average of 2.6%. Inadequate drug use and poor patient compliance increase MDR-TB prevalence through selective pressure. Therefore, prompt detection of drug resistance in tuberculosis patients at the time of diagnosis and quantitative monitoring of these resistant strains during treatment are crucial.
METHODS: A multiplex droplet digital PCR (ddPCR) assay was developed and assessed using DNA material of nine Mycobacterium tuberculosis strains with known mutation status that were purchased from the Korean National Tuberculosis Association. We collected a total of 18 MDR-TB residual samples referred for PCR

analysis. Total DNA was extracted from the samples and subjected to the quadruplex ddPCR assay. Their results were compared to those of known resistance phenotypes.
RESULTS: The analytical sensitivity and specificity of the multiplex ddPCR assay for detecting INH, RIF, EMB, FQ, and SM resistance-causing mutations ranged from 71.43 to 100% and 94.12-100%, respectively. Follow-up sample results showed that the quadruplex ddPCR assay was sensitive enough to detect IS6110 and other mutations even after onset of treatment.
CONCLUSIONS: We developed a sensitive and accurate multiplex ddPCR assay that can detect the presence of tuberculosis quantitatively and resistance-conveying mutations concurrently. This tool could aid clinicians in the diagnosis and treatment monitoring of tuberculosis.

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

24. Treatment Outcomes of Fluoroquinolone-Resistant Multidrug-Resistant Tuberculosis: An Implication for Delamanid.

Tuberc Respir Dis (Seoul). 2024 Apr;87(2):206-208. doi: 10.4046/trd.2023.0188. Epub 2023 Dec 18.

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Comment in
Tuberc Respir Dis (Seoul). 2024 Apr;87(2):209-211.

Comment on
Tuberc Respir Dis (Seoul). 2024 Jan 30;:

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PMID: 38111099

Conflict of interest statement: Conflicts of Interest No potential conflict of interest relevant to this article was reported.

25. A pragmatic randomized controlled trial to evaluate the efficacy and safety of an oral short-course regimen including bedaquiline for the treatment of patients with multidrug-resistant tuberculosis in China: study protocol for PROSPECT.

Trials. 2024 Apr 1;25(1):227. doi: 10.1186/s13063-024-07946-9.

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INTRODUCTION: The lack of safe, effective, and simple short-course regimens (SCRs) for multidrug-resistant/rifampicin-resistant tuberculosis (MDR/RR-TB) treatment has significantly impeded TB control efforts in China.
METHODS: This phase 4, randomized, open-label, controlled, non-inferiority trial aims to assess the efficacy and safety of a 9-month all-oral SCR containing bedaquiline (BDQ) versus an all-oral SCR without BDQ for adult MDR-TB patients (18-65 years) in China. The trial design mainly mirrors that of the "Evaluation of a Standardized Treatment Regimen of Anti-Tuberculosis Drugs for Patients with MDR-TB" (STREAM) stage 2 study, while also incorporating programmatic data from South Africa and the 2019 consensus recommendations of Chinese MDR/RR-TB treatment experts. Experimental arm participants will receive a modified STREAM regimen C that replaces three group C drugs, ethambutol (EMB), pyrazinamide (PZA), and prothionamide (PTO), with two group B drugs, linezolid (LZD) and cycloserine (CS), while omitting high-dose isoniazid (INH) for confirmed INH-resistant cases. BDQ duration will be extended from 6 to 9 months for participants with Mycobacterium tuberculosis-positive sputum cultures at week 16. The control arm will receive a modified STREAM regimen B without high-dose INH and injectable kanamycin (KM) that incorporates experimental arm LZD and CS dosages, treatment durations, and administration methods. LZD (600 mg) will be given daily for ≥ 24 weeks as guided by observed benefits and harm. The primary outcome measures the proportion of participants with favorable treatment outcomes at treatment completion (week 40), while the same measurement taken at 48 weeks post-treatment completion is the secondary outcome. Assuming an $\alpha = 0.025$ significance level (one-sided test), 80% power, 15% non-inferiority margin, and 10% lost to follow-up rate, each arm requires 106 participants (212 total) to demonstrate non-inferiority.
DISCUSSION: PROSPECT aims to assess the safety and efficacy of a BDQ-containing SCR MDR-TB treatment at seventeen sites across China, while also providing high-quality data to guide SCRs administration under the direction of the China National Tuberculosis Program for MDR-TB. Additionally, PROSPECT will explore the potential benefits of extending the administration of the 9-month BDQ-containing SCR for participants without sputum conversion by week 16.
TRIAL REGISTRATION: ClinicalTrials.gov NCT05306223. Prospectively registered on 16 March 2022 at https://clinicaltrials.gov/ct2/show/NCT05306223?term=NCT05306223&draw=1&rank=1 {2}.

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PMID: 38561815 [Indexed for MEDLINE]

Conflict of interest statement: GJT, GMQ, DJ, PY, LYH, ZY, and LL declare that

they have no competing interests. GM, NL, NB, and JYX are employees of Janssen participating in the development of bedaquiline.

26. Frequency, management and impact of adverse events on treatment outcomes in patients with multidrug resistant tuberculosis in Balochistan, Pakistan.

J Pharm Policy Pract. 2024 Apr 2;17(1):2332878. doi: 10.1080/20523211.2024.2332878. eCollection 2024.

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BACKGROUND: Early detection, monitoring, and managing adverse events (AEs) are crucial in optimising treatment for multidrug-resistant tuberculosis (MDR-TB) patients.
OBJECTIVES: To investigate the incidence, factors, management, and impact of AEs on treatment outcomes in MDR-TB patients.
METHODS: This study reviewed the medical records of 275 MDR-TB patients at Fatimah Jinnah Institute of Chest Diseases in Quetta, Pakistan. Patient information was collected using a designed data collection form. Mann-Whitney U and Kruskal-Wallis tests examined the difference in AEs occurrences based on patients' characteristics. Multiple binary logistic regression identified factors associated with unsuccessful outcomes, with statistical significance set at a p-value < 0.05.
RESULTS: Almost all patients (99.6%) experienced at-least one AE (median = 4/patient, interquartile range:3-6). The most common were GI disturbance (95.3%), arthralgia (80.4%), body pain and headache (61.8%), ototoxicity (61.4%), psychiatric disturbance (44%), hypokalaemia (40.4%), dermatological reactions (26.2%) and hypothyroidism (21.5%). AEs led to treatment modification in 7.3% patients. Educated patients, those with a history of TB treatment, previous use and resistance to any second-line drug had significantly higher number of AEs. A total of 64.0% were declared cured, 3.6% completed treatment, 19.6% died and 12.7.9% were lost to follow-up. Patients'

age of 41-60(OR = 9.225) and >60 years(OR = 23.481), baseline body weight of 31-60 kg(OR = 0.180), urban residence(OR = 0.296), and experiencing ototoxicity (OR = 0.258) and hypothyroidism (OR = 0.136) were significantly associated with unsuccessful treatment outcomes.
CONCLUSION: AEs were highly prevalent but did not negatively impact treatment outcomes. Patients at higher risk of developing AEs and unsuccessful outcomes should receive special attention for its early management.

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PMCID: PMC10989201
PMID: 38572376

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27. Prevalence, Clinical Features, and Predictors of Adrenal Insufficiency in Adults With Tuberculosis or HIV: A Systematic Review and Meta-analysis.

Open Forum Infect Dis. 2024 Feb 22;11(4):ofae098. doi: 10.1093/ofid/ofae098. eCollection 2024 Apr.

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BACKGROUND: Despite the high frequency of adrenal insufficiency (AI) in patients

with tuberculosis or HIV, its diagnosis is often missed or delayed resulting in increased mortality. This systematic review and meta-analysis aimed to document the prevalence, significant clinical features, and predictors of AI in adult patients with tuberculosis or HIV.
METHODS: We systematically searched databases (Medline, Embase, CINAHL, Cochrane Library, and Africa Journal Online) for published studies on AI in adult patients with tuberculosis or HIV. The pooled prevalence of AI was determined by a random-effect model meta-analysis. A narrative review was used to describe the significant clinical features and predictors of AI in adult patients with tuberculosis or HIV.
RESULTS: A total of 46 studies involving 4044 adults were included: 1599 with tuberculosis and 2445 with HIV. The pooled prevalence of AI was 33% (95% CI, 22%-45%; I2 = 97.7%, P < .001) in participants with tuberculosis and 28% (95% CI, 18%-38%; I2 = 98.9%, P < .001) in those with HIV. Presentation with multidrug-resistant tuberculosis, abdominal pain, salt craving, myalgia, increased severity and duration of tuberculosis disease, and the absence of nausea predicted AI in participants with tuberculosis in 4 studies. Cytomegalovirus antigenemia positivity, rifampicin therapy, and eosinophilia >3% predicted AI in participants with HIV in 2 studies.
CONCLUSIONS: AI is relatively common in adults with tuberculosis or HIV. Its timely screening, diagnosis, and management in patients with these 2 conditions should be encouraged to avert mortality.

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PMID: 38560601

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

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

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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.

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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.

29. Identification of Mycobacterium tuberculosis Resistance to Common Antibiotics: An Overview of Current Methods and Techniques.

Infect Drug Resist. 2024 Apr 12;17:1491-1506. doi: 10.2147/IDR.S457308. eCollection 2024.

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Multidrug-resistant tuberculosis (MDR-TB) is an essential cause of tuberculosis treatment failure and death of tuberculosis patients. The rapid and reliable profiling of Mycobacterium tuberculosis (MTB) drug resistance in the early stage is a critical research area for public health. Then, most traditional approaches for detecting MTB are time-consuming and costly, leading to the inappropriate therapeutic schedule resting on the ambiguous information of MTB drug resistance, increasing patient economic burden, morbidity, and mortality. Therefore, novel diagnosis methods are frequently required to meet the emerging challenges of MTB drug resistance distinguish. Considering the difficulty in treating MDR-TB, it is urgently required for the development of rapid and accurate methods in the identification of drug resistance profiles of MTB in clinical diagnosis. This review discussed recent advances in MTB drug resistance detection, focusing on developing emerging approaches and their applications in tangled clinical situations. In particular, a brief overview of antibiotic resistance to MTB was present, referred to as intrinsic bacterial resistance,

consisting of cell wall barriers and efflux pumping action and acquired resistance caused by genetic mutations. Then, different drug susceptibility test (DST) methods were described, including phenotype DST, genotype DST and novel DST methods. The phenotype DST includes nitrate reductase assay, RocheTM solid ratio method, and liquid culture method and genotype DST includes fluorescent PCR, GeneXpert, PCR reverse dot hybridization, ddPCR, next-generation sequencing and gene chips. Then, novel DST methods were described, including metabolism testing, cell-free DNA probe, CRISPR assay, and spectral analysis technique. The limitations, challenges, and perspectives of different techniques for drug resistance are also discussed. These methods significantly improve the detection sensitivity and accuracy of multidrug-resistant tuberculosis (MRT) and can effectively curb the incidence of drug-resistant tuberculosis and accelerate the process of tuberculosis eradication.

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PMID: 38628245

Conflict of interest statement: The authors declare that the research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

30. PASS to End TB in Europe: Accelerated efforts on prevention and systematic screening to end tuberculosis in the WHO European Region by 2030.

Int J Infect Dis. 2024 Apr;141S:106980. doi: 10.1016/j.ijid.2024.02.023. Epub 2024 Feb 23.

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OBJECTIVES: Outline the objectives, methods, and initial stages of the Prevention and Systematic Screening (PASS) initiative, a complimentary element of the innovative new approach of technical assistance mechanisms of WHO and its partners to countries aligned to the Regional TB Action Plan to End TB in the European Region by 2030.
DESIGN: To provide an objective and critical overview of the existing landscape on TB epidemic in the WHO European Region (the European Region) and ii) identify the strategic significance of proactive measures aimed at approaching TB pre-elimination in the Region.
RESULTS: Interventions primarily include systematic screening for TB disease and treatment for TB infection (TBI).
CONCLUSIONS: PASS to End TB is an exemplary initiative of how technical and funding partners are joining hands to support national health programmes to work towards global commitments to curb major public health challenges like TB.

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PMID: 38403111 [Indexed for MEDLINE]

31. Tuberculosis patients face high treatment support costs in Colombia, 2021.

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OBJECTIVE: To estimate the baseline to measure one of the three indicators of the World Health Organization (WHO) End TB strategy (2015-2035), measure the costs incurred by patients affected by tuberculosis (TB) during a treatment episode and estimate the proportion of households facing catastrophic costs (CC) and associated risk factors, in Colombia, 2021.
MATERIAL AND METHODS: A nationally representative cross-sectional survey was conducted among participants on TB treatment in Colombia, using telephone interviews due to the exceptional context of the COVID-19 pandemic. The survey collected household costs (direct [medical and non-medical out-of-pocket expenses] and indirect) over an episode of TB, loss of time, coping measures, self-reported income, and asset ownership. Total costs were expressed as a proportion of annual household income and analyzed for risk factors of CC (defined as costs above 20% annual household income).
RESULTS: The proportion of TB-affected households incurring in costs above 20% annual household income (CC) was 51.7% (95%CI: 45.4-58.0) overall, 51.3% (95%CI: 44.9-57.7) among patients with drug-sensitive (DS) TB, and 65.0% (95%CI: 48.0-82.0) among drug-resistant (DR). The average patient cost of a TB case in Colombia was $1,218 (95%CI 1,106-1,330) including $860.9 (95%CI 776.1-945.7) for non-medical costs, $339 (95%CI 257-421) for the indirect costs, and $18.1 (95%CI 11.9-24.4) for the medical costs. The factors that influenced the probability of facing CC were income quintile, job loss, DR-TB patient, and TB type.
CONCLUSION: Main cost drivers for CC were non-medical out-of-pocket expenses and income loss (indirect costs). Current social protection programs ought to be expanded to mitigate the proportion of TB-affected households facing CC in Colombia, especially those with lower income levels.

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

32. Treatment Outcomes of Fluoroquinolone- Resistant Multidrug-Resistant Tuberculosis: An Implication for Delamanid - Authors' Reply.

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DOI: 10.4046/trd.2024.0010
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PMID: 38287482

Conflict of interest statement: Conflicts of Interest No potential conflict of interest relevant to this article was reported.

33. Bactericidal and sterilizing activity of novel regimens combining bedaquiline or TBAJ-587 with GSK2556286 and TBA-7371 in a mouse model of tuberculosis.

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The combination of bedaquiline, pretomanid, and linezolid (BPaL) has become a preferred regimen for treating multidrug- and extensively drug-resistant tuberculosis (TB). However, treatment-limiting toxicities of linezolid and reports of emerging bedaquiline and pretomanid resistance necessitate efforts to develop new short-course oral regimens. We recently found that the addition of GSK2556286 increases the bactericidal and sterilizing activity of BPa-containing regimens in a well-established BALB/c mouse model of tuberculosis. Here, we used this model to evaluate the potential of new regimens combining bedaquiline or the more potent diarylquinoline TBAJ-587 with GSK2556286 and the DprE1 inhibitor TBA-7371, all of which are currently in early-phase clinical trials. We found the combination of bedaquiline, GSK2556286, and TBA-7371 to be more active than the first-line regimen and nearly as effective as BPaL in terms of bactericidal and sterilizing activity. In addition, we found that GSK2556286 and TBA-7371 were as effective as pretomanid and the novel oxazolidinone TBI-223 when either drug pair was combined with TBAJ-587 and that the addition of GSK2556286 increased the bactericidal activity of the TBAJ-587, pretomanid, and TBI-223 combination. We conclude that GSK2556286 and TBA-7371 have the potential to replace pretomanid, an oxazolidinone, or both components, in combination with bedaquiline or TBAJ-587.

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

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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.

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35. Targeted sequencing from cerebrospinal fluid for rapid identification of drug-resistant tuberculous meningitis.

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Mortality from tuberculous meningitis (TBM) remains around 30%, with most deaths occurring within 2 months of starting treatment. Mortality from drug-resistant strains is higher still, making early detection of drug resistance (DR) essential. Targeted next-generation sequencing (tNGS) produces high read depths, allowing the detection of DR-associated alleles with low frequencies. We applied Deeplex Myc-TB-a tNGS assay-to cerebrospinal fluid (CSF) samples from 72 adults with microbiologically confirmed TBM and compared its genomic drug susceptibility predictions to a composite reference standard of phenotypic susceptibility testing (pDST) and whole genome sequencing, as well as to clinical outcomes. Deeplex detected Mycobacterium tuberculosis complex DNA in 24/72 (33.3%) CSF samples and generated full DR reports for 22/24 (91.7%). The read depth generated by Deeplex correlated with semi-quantitative results from MTB/RIF Xpert. Alleles with <20% frequency were seen at canonical loci associated with first-line DR. Disregarding these low-frequency alleles, Deeplex had 100% concordance with the composite reference standard for all drugs except pyrazinamide and streptomycin. Three patients had positive CSF cultures after 30 days of treatment; reference tests and Deeplex identified isoniazid resistance in two, and Deeplex alone identified low-frequency rifampin resistance alleles in one. Five patients died, of whom one had pDST-identified pyrazinamide resistance. tNGS on CSF can rapidly and accurately detect drug-resistant TBM, but its application is limited to those with higher bacterial loads. In those with lower bacterial burdens, alternative approaches need to be developed for both diagnosis and resistance detection.

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36. Identifying local foci of tuberculosis transmission in Moldova using a spatial

multinomial logistic regression model.

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BACKGROUND: Multidrug resistant tuberculosis (MDR-TB) represents a major public health concern in the Republic of Moldova, with an estimated 31% of new and 56% of previously treated TB cases having MDR disease in 2022. A recent genomic epidemiology study of incident TB occurring in 2018 and 2019 found that 92% of MDR-TB was the result of transmission. The MDR phenotype was concentrated among two M. tuberculosis (Mtb) lineages: L2.2.1 (Beijing) and L4.2.1 (Ural).
METHODS: We developed and applied a hierarchical Bayesian multinominal logistic regression model to Mtb genomic, spatial, and epidemiological data collected from all individuals with diagnosed TB in Moldova in 2018 and 2019 to identify locations in which specific Mtb strains are being transmitted. We then used a logistic regression model to estimate locality-level factors associated with local transmission.
FINDINGS: We found differences in the spatial distribution and degree of local concentration of disease due to specific strains of Beijing and Ural lineage Mtb. Foci of transmission for four strains of Beijing lineage Mtb, predominantly of the MDR-TB phenotype, were located in several regions, but largely concentrated in Transnistria. In contrast, transmission of Ural lineage Mtb had less marked patterns of spatial aggregation, with a single strain (also of the MDR phenotype) spatially clustered in southern Transnistria. We found a 30% (95% credible interval 2%-80%) increase in odds of a locality being a transmission cluster for each increase of 100 persons per square kilometer, while higher local tuberculosis incidence and poverty were not associated with a locality being a transmission focus.
INTERPRETATION: Our results identified localities where specific Mtb transmission networks were concentrated and quantified the association between locality-level factors and focal transmission. This analysis revealed Transnistria as the primary area where specific Mtb strains (predominantly of

the MDR-TB phenotype) were locally transmitted and suggests that targeted intensified case finding in this region may be an attractive policy option.
FUNDING: Funding for this work was provided by the National Institute of Allergy and Infectious Diseases at the US National Institutes of Health.

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

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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.

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38. A systematic efficacy analysis of tuberculosis treatment with BPaL-containing regimens using a multiscale modeling approach.

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Tuberculosis (TB) is a life-threatening infectious disease. The standard treatment is up to 90% effective; however, it requires the administration of four antibiotics (isoniazid, rifampicin, pyrazinamide, and ethambutol [HRZE]) over long time periods. This harsh treatment process causes adherence issues for patients because of the long treatment times and a myriad of adverse effects. Therefore, the World Health Organization has focused goals of shortening standard treatment regimens for TB in their End TB Strategy efforts, which aim to reduce TB-related deaths by 95% by 2035. For this purpose, many novel and promising combination antibiotics are being explored that have recently been discovered, such as the bedaquiline, pretomanid, and linezolid (BPaL) regimen. As a result, testing the number of possible combinations with all possible novel regimens is beyond the limit of experimental resources. In this study, we present a unique framework that uses a primate granuloma modeling approach to screen many combination regimens that are currently under clinical and experimental exploration and assesses their efficacies to inform future studies. We tested well-studied regimens such as HRZE and BPaL to evaluate the validity and accuracy of our framework. We also simulated additional promising combination regimens that have not been sufficiently studied clinically or experimentally, and we provide a pipeline for regimen ranking based on their efficacies in granulomas. Furthermore, we showed a correlation between simulation rankings and new marmoset data rankings, providing evidence for the credibility of our framework. This framework can be adapted to any TB regimen and can rank any number of single or combination regimens.

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39. Genetic mechanisms of co-emergence of INH-resistant Mycobacterium tuberculosis strains during the standard course of antituberculosis therapy.

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The incidence of isoniazid (INH) resistant Mycobacterium tuberculosis is increasing globally. This study aimed to identify the molecular mechanisms behind the development of INH resistance in M. tuberculosis strains collected from the same patients during the standard course of treatment. Three M. tuberculosis strains were collected from a patient before and during antituberculosis (anti-TB) therapy. The strains were characterized using phenotypic drug susceptibility tests, Mycobacterial Interspersed Repeated Unit-Variable-Number Tandem Repeats (MIRU-VNTR), and whole-genome sequencing (WGS) to identify mutations associated with INH resistance. To validate the role of the novel mutations in INH resistance, the mutated katG genes were electroporated into a KatG-deleted M. tuberculosis strain (GA03). Three-dimensional structures of mutated KatG were modeled to predict their impact on INH binding. The pre-treatment strain was susceptible to INH. However, two INH-resistant strains were isolated from the patient after anti-TB therapy. MIRU-VNTR and WGS revealed that the three strains were clonally identical. A missense mutation (P232L) and a nonsense mutation (Q461Stop) were identified in

the katG of the two post-treatment strains, respectively. Transformation experiments showed that katG of the pre-treatment strain restored INH susceptibility in GA03, whereas the mutated katG genes from the post-treatment strains rendered negative catalase activity and INH resistance. The protein model indicated that P232L reduced INH-KatG binding affinity while Q461Stop truncated gene transcription. Our results showed that the two katG mutations, P232L and Q461Stop, accounted for the co-emergence of INH-resistant clones during anti-TB therapy. The inclusion of these mutations in the design of molecular assays could increase the diagnostic performance.IMPORTANCEThe evolution of drug-resistant strains of Mycobacterium tuberculosis within the lung lesions of a patient has a detrimental impact on treatment outcomes. This is particularly concerning for isoniazid (INH), which is the most potent first-line antimycobacterial drug. However, the precise genetic factors responsible for drug resistance in patients have not been fully elucidated, with approximately 15% of INH-resistant strains harboring unknown genetic factors. This raises concerns about the emergence of drug-resistant clones within patients, further contributing to the global epidemic of resistance. In this study, we revealed the presence of two novel katG mutations, which emerged independently due to the stress exerted by antituberculosis (anti-TB) treatment on a parental strain. Importantly, we experimentally demonstrated the functional significance of both mutations in conferring resistance to INH. Overall, this research sheds light on the genetic mechanisms underlying the evolution of INH resistance within patients and provides valuable insights for improving diagnostic performance by targeting specific mutations.

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

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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.

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PMID: 38590765

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41. War related disruption of clinical tuberculosis services in Tigray, Ethiopia during the recent regional conflict: a mixed sequential method study.

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BACKGROUND: More than 70% of the health facilities in Tigray, northern Ethiopia, have been totally or partially destroyed by the recent war in the region. Diagnosis and management of tuberculosis were among many health services that suffered. In this study we assess the status of tuberculosis care in health facilities of Tigray during the recent war and compare it with the immediate pre-war state.
METHODS: Using sequential mixed method, we analyzed and compared the availability of diagnostic services in 69 health facilities and the utilization of tuberculosis care in 50 of them immediately before the war (September-October 2020) and during the war (November-July 2021). TB focal persons in each selected health facility were interviewed to evaluate the status of diagnostic services.

Patient service utilization was assessed using health facility registrations. We also compared the average monthly case detection rate of multidrug resistant tuberculosis in the region before and during the war. We computed summary statistics and performed comparisons using t-tests. Finally, existing challenges related to tuberculosis care in the region were explored via in-depth interviews. Two investigators openly coded and analyzed the qualitative data independently via thematic analysis.
RESULTS: Among the 69 health facilities randomly selected, the registers of 19 facilities were destroyed by the war; data from the remaining 50 facilities were included in the TB service utilization analysis. In the first month of the war (November 2021) the number of tuberculosis patients visiting health facilities fell 34%. Subsequently the visitation rate improved steadily, but not to pre-war rates. This reduction was significant in northwest, central and eastern zones. Tuberculosis care in rural areas was hit hardest. Prior to the war 60% of tuberculosis patients were served in rural clinics; this number dropped to an average of 17% during the war. Health facilities were systematically looted. Of the 69 institutions assessed, over 69% of the microscopes in health centers, 87.5% of the microscopes in primary hospitals, and 68% of the microscopes in general hospitals were stolen or damaged. Two GeneXpert nucleic acid amplification machines were also taken from general hospitals. Regarding drug resistant TB, the average number of multidrug resistant tuberculosis (MDR TB) cases detected per month was reduced by 41% during the war with p-value < 0.001. In-depth interviews with eight health care workers indicated that the main factors affecting tuberculosis care in the area were lack of security, health facility destruction, theft of essential equipment, and drug supply disruption.
CONCLUSION AND RECOMMENDATION: Many tuberculosis patients failed to visit health facilities during the war. There was substantial physical damage to health care facilities and systematic looting of diagnostic equipment. Restoring basic public services and revitalizing clinical care for tuberculosis need urgent consideration.

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42. Sub-MIC levels of bedaquiline and clofazimine can select Mycobacterium tuberculosis mutants with increased MIC.

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Multidrug-resistant tuberculosis (MDR-TB) patients not cured at the time of stopping treatment are exposed to Minimum Inhibitory Concentration (MIC) and sub-MIC levels for many months after discontinuing bedaquiline (BDQ) or clofazimine (CFZ) treatment. In vitro cultures treated with BDQ and CFZ sub-MIC concentrations clearly showed enrichment in the Rv0678 mutant population, demonstrating that pre-existing Rv0678 mutants can be selected by sub-MIC concentrations of BDQ and CFZ if not protected by an alternative MDR-TB treatment.

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43. A robust computational quest: Discovering potential hits to improve the treatment of pyrazinamide-resistant Mycobacterium tuberculosis.

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The rise of pyrazinamide (PZA)-resistant strains of Mycobacterium tuberculosis (MTB) poses a major challenge to conventional tuberculosis (TB) treatments. PZA, a cornerstone of TB therapy, must be activated by the mycobacterial enzyme pyrazinamidase (PZase) to convert its active form, pyrazinoic acid, which

targets the ribosomal protein S1. Resistance, often associated with mutations in the RpsA protein, complicates treatment and highlights a critical gap in the understanding of structural dynamics and mechanisms of resistance, particularly in the context of the G97D mutation. This study utilizes a novel integration of computational techniques, including multiscale biomolecular and molecular dynamics simulations, physicochemical and medicinal chemistry predictions, quantum computations and virtual screening from the ZINC and Chembridge databases, to elucidate the resistance mechanism and identify lead compounds that have the potential to improve treatment outcomes for PZA-resistant MTB, namely ZINC15913786, ZINC20735155, Chem10269711, Chem10279789 and Chem10295790. These computational methods offer a cost-effective, rapid alternative to traditional drug trials by bypassing the need for organic subjects while providing highly accurate insight into the binding sites and efficacy of new drug candidates. The need for rapid and appropriate drug development emphasizes the need for robust computational analysis to justify further validation through in vitro and in vivo experiments.

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

44. Evaluation of a population-wide, systematic screening initiative for tuberculosis on Daru island, Western Province, Papua New Guinea.

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BACKGROUND: A population-wide, systematic screening initiative for tuberculosis (TB) was implemented on Daru island in the Western Province of Papua New Guinea, where TB is known to be highly prevalent. The initiative used a mobile van equipped with a digital X-ray device, computer-aided detection (CAD) software to identify TB-related abnormalities on chest radiographs, and GeneXpert machines for follow-on diagnostic testing. We describe the results of the TB screening initiative, evaluate its population-level impact and examine risk factors associated with TB detection.
METHODS: Through a retrospective review of screening data, we assessed the effectiveness of the screening by examining the enrolment coverage and the proportion of people with TB among screened subjects. A cascade analysis was performed to illustrate the flow of participants in the screening algorithm. We conducted univariate and multivariate analyses to identify factors associated with TB. Furthermore, we estimated the number of additional cases detected by the project by examining the trend of routine TB case notifications during the intervention period, compared to the historical baseline cases and trend-adjusted expected cases.
RESULTS: Of the island's 18,854 residents, 8,085 (42.9%) were enrolled and 7,970 (98.6%) had chest X-ray interpreted by the CAD4TB software. A total of 1,116 (14.0%) participants were considered to have abnormal CXR. A total of 69 Xpert-positive cases were diagnosed, resulting in a detection rate of 853 per 100 000 population screened. 19.4% of people with TB had resistance to rifampicin. People who were in older age groups (aOR 6.6, 95%CI: 1.5-29.1 for the 45-59 age group), were severely underweight (aOR 2.5, 95%CI:1.0-6.1) or underweight (aOR 2.1, 95%CI: 1.1-3.8), lived in households < 5 people (aOR 3.4, 95%CI:1.8-6.6) and had a past history of TB (aOR 2.1, 95%CI: 1.2-3.6) were more likely to have TB. The number of bacteriologically confirmed TB notified during the intervention period was 79.3% and 90.8% higher than baseline notifications and forecasted notifications, respectively.
CONCLUSION: The screening project demonstrated its effectiveness with the high Xpert-positive TB prevalence among the participants and by successfully yielding additional cases of bacteriologically confirmed TB including rifampicin-resistant TB. The results and lessons learnt from the project should inform future TB screening initiatives in Papua New Guinea.

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45. Interaction of eugenol-based anti-tuberculosis nanoemulsion with bovine serum albumin: A spectroscopic study including Rifampicin, Isoniazid, Pyrazinamide, and Ethambutol.

Heliyon. 2024 Mar 19;10(7):e28306. doi: 10.1016/j.heliyon.2024.e28306. eCollection 2024 Apr 15.

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Tuberculosis (TB), a deadly infectious disease, is primarily caused by the bacterium Mycobacterium tuberculosis. The misuse of antibiotics has led to the development of drug resistance, prompting researchers to explore new technologies to combat multidrug-resistant Tuberculosis (MDR TB). Phospholipid-based nanotherapeutics, such as nanoemulsions, are gaining traction as they enhance drug solubility, stability, and bioavailability. Our study focuses on the interaction between Bovine Serum Albumin (BSA) and a drug-loaded nanoemulsion based on Eugenol. This nanoemulsion incorporates Eugenol, Clove, cinnamon oil, and first-line anti-tuberculosis drugs like Rifampicin, Isoniazid, Pyrazinamide, and Ethambutol. The primary objective is to assess the biosafety profile of the nanoemulsion upon interaction with BSA. We employed Fluorescence, UV-visible, and Fourier Transform Infrared Spectroscopy (FTIR) to analyze this interaction. UV-visible spectroscopy detected changes in hydrophobicity due to structural alterations in BSA near the tryptophan residue, leading to the formation of ground-state complexes. Fluorescence spectroscopy demonstrated that the nanoemulsion effectively quenched fluorescence originating from tryptophan

and tyrosine residues. Studies using synchronous and three-dimensional spectroscopy point to a potential modification of the aromatic environment of BSA by the nanoemulsion. Resonance light scattering spectra indicated the formation of large aggregates due to the interaction with the nanoemulsion. The second derivative FTIR spectra showed an increase in the magnitude of secondary structure bands, suggesting a conformational shift. This research has significant pharmacological implications for developing safer, more targeted drug delivery systems. The information obtained from the interaction of the nanoemulsion with the blood carrier protein is vital for the future development of superior carriers with minimal adverse effects on patients. It is crucial to remember that conformational changes brought on by drug-ligand complexes attaching to carrier proteins may have negative consequences. Therefore, this study enhances the in vitro evaluation of potential adverse effects of the nanoemulsion on serum proteins.

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PMID: 38571616

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46. Discordance in Phenotypic and Genotypic Susceptibility Testing for Streptomycin Due to Nonsynonymous/Nonsense/Deletion Frame-Shift Mutations in Gidb Among Clinical Mycobacterium tuberculosis Isolates in Kuwait.

Med Princ Pract. 2024 Apr 1. doi: 10.1159/000538584. Online ahead of print.

Al-Mutairi NM, Ahmad S, Mokaddas E.

OBJECTIVE: Increasing reports of resistance to newer anti-tuberculosis drugs have prompted the search for other alternative drugs. Streptomycin could be used for the treatment of drug-resistant tuberculosis if susceptibility of Mycobacterium tuberculosis isolate to streptomycin could be accurately detected. We performed phenotypic and genotypic drug susceptibility testing (DST) of 118 M. tuberculosis isolates for streptomycin.
MATERIALS AND METHODS: Fifty pansusceptible and 68 multidrug-resistant M. tuberculosis (MDR-TB) isolates were used. Phenotypic DST for streptomycin, rifampicin, isoniazid and ethambutol was performed by mycobacteria growth indicator tube (MGIT) 960 System. Genotypic DST was done by GenoTypeMTBDRplus

assay for rifampicin and isoniazid and by PCR-sequencing of rpsL, rrs and gidB genes for streptomycin. MDR-TB isolates were genotyped by spoligotyping.
RESULTS: Phenotypic DST identified 50 isolates susceptible to all four drugs (pansusceptible). Sixty-one of 68 MDR-TB isolates were resistant to streptomycin. Genotypic testing for rifampicin and isoniazid yielded expected results. Fifty pansusceptible and 7 streptomycin-susceptible MDR-TB isolates contained no mutation in rpsL or rrs, while 47, 2 and 1 STR-resistant isolate contained rpsL, rrs and rpsL + rrs mutations, respectively. Of the remaining 11 STR-resistant MDR-TB, 9 isolates contained deletion frame-shift/nonsynonymous mutations in gidB. Surprisingly, 13 pansusceptible isolates also contained deletion frame-shift/nonsense/nonsynonymous mutations in gidB. Also, 30 of 68 MDR-TB but only 2 of 50 pansusceptible isolates belonged to the Beijing genotype.
CONCLUSIONS: Our data show that, like ifampicin, ethambutol and pyrazinamide, streptomycin also exhibits discordant phenotypic and genotypic DST results for some M. tuberculosis isolates. Hence, streptomycin should be included in therapy regimens only if both phenotypic and genotypic resistance testing indicate susceptibility to avoid amplification of resistance and drug toxicity.

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PMID: 38560979

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

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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
PMID: 38597637

48. Monitoring of First-line Drug Resistance Mutations Outside the Scope of Xpert MTB/RIF Ultra is Needed for Successful Control of DR-TB in Southern Mozambique.

Clin Infect Dis. 2024 Apr 10;78(4):842-845. doi: 10.1093/cid/ciad684.

Mariner-Llicer C(1), Saavedra Cervera B(2)(3), Mambuque E(3), Gomes N(3), Munguambe S(3), Villamayor L(4), Cancino-Muñoz I(4)(5), Torres-Puente M(1), Nguenha D(3)(6), Respeito D(3), Tembe G(3), López MG(1), Comas I(1)(7), García-Basteiro AL(2)(3)(8).

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Multidrug-resistant(MDR) tuberculosis in Southern Africa is of great concern, exacerbated by the spread of a clone harboring a mutation missed by Xpert Ultra. In Southern Mozambique, the presence of such mutation and rising cases of non-MDR isoniazid resistance highlights the need to ensure accurate detection of antimicrobial-resistance in the country.

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49. A pregnant woman with pre-XDR PTB giving birth to a healthy newborn: A case report.

Heliyon. 2024 Mar 24;10(7):e28530. doi: 10.1016/j.heliyon.2024.e28530.

eCollection 2024 Apr 15.

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We reported a late-pregnancy woman with pre-XDR PTB who had not received regular anti-tuberculosis treatment prior to delivery. Despite this, she successfully delivered a premature baby who exhibited normal growth and development, and subsequently completed her anti-tuberculosis treatment. This report suggests that delayed treatment for pre-XDR TB during late pregnancy does not necessarily increase the risk of treatment failure for the mother or the risk of neonatal tuberculosis.

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PMCID: PMC10988000
PMID: 38571639

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.

50. 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.

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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.

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PMID: 38442538 [Indexed for MEDLINE]

51. Poor performance of paired tests of latent tuberculosis in highly immune-compromised individuals exposed to multidrug-resistant tuberculosis: time for new diagnostic markers.

ERJ Open Res. 2024 Apr 8;10(2):00732-2023. doi: 10.1183/23120541.00732-2023. eCollection 2024 Mar.

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Guideline-based recommendations for diagnosis of latent TB in highly immune suppressed populations are difficult to interpret and poorly characterised. More accurate biomarkers independent of T-cell functions are urgently required. https://bit.ly/41P8vTa.

DOI: 10.1183/23120541.00732-2023
PMCID: PMC11000274
PMID: 38590937

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

52. Spiritual Holy Water Sites in Ethiopia: Unrecognized High-Risk Settings for Transmission of Pulmonary Tuberculosis.

Int J Microbiol. 2024 Apr 8;2024:3132498. doi: 10.1155/2024/3132498. eCollection 2024.

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Ethiopia is a high-tuberculosis (TB) burden country with 157 new cases per 100,000 people, with 23,800 TB-related deaths in 2020. In Ethiopia, TB patients have different healthcare-seeking behaviors. They frequently visit spiritual places, such as holy water sites (HWSs), to seek treatment for their illness spiritually. This study examined the prevalence of pulmonary TB (PTB) and drug susceptibility profiles of Mycobacterium tuberculosis (MTB) isolates among spiritual HWS attendees in Northwest Ethiopia. A cross-sectional study was conducted from June 2019 to March 2020. Sputum samples were collected, processed, and cultured using Löwenstein-Jensen (LJ) culture medium. Second-generation line probe assays (LPAs), GenoType®MTBDRplus VER2.0 and GenoType®MTBDRsl VER2.0, were used to detect anti-TB drug-resistant isolates. STATA 17 was utilized to perform descriptive statistics, bivariate, and multivariate regression analyses. Of 560 PTB-symptomatic participants, 21.8% ((95% confidence interval (95 CI): 18.4-25.2%)) were culture-positive, resulting in a point prevalence of 1,183/100,000 attendees. Amongst HWS attendees, culture-positive TB occurred most commonly in persons 18-33 years of age (28.5% (95 CI 23.4-34.3%)). Other participant characteristics significantly associated with culture-positive PTB were as follows: rural residents (adjusted odds ratio (aOR) 2.65; 95 CI 1.38-5.10), married participants (aOR 2.43; 95 CI 1.28-4.63), family members >5 per household (aOR 1.84; 95 CI 1.04-3.24), and sharing living space (aOR 10.57; 95 CI 3.60-31.13). Also, among 438 participants followed for 12 months after showing negative TB culture results while at the HWS, 6.8% (95 CI 4.4-9.4%) developed or contracted culture-positive TB post-residency at the HWSs. Of the 122 tested isolates, 20 (16.4%) were isoniazid (INH) and/or rifampicin (RIF) resistant. Multidrug-resistant (MDR) TB was detected in 15 cases (12.3%), five of which were fluoroquinolones (FLQs) resistant. The findings from this study should raise a concern about HWSs as potential high-risk settings for TB transmission. It is recommended that appropriate control measures be instituted that include compulsory TB testing and tightened infection control at HWSs, where an increased risk exists for transmission of TB.

DOI: 10.1155/2024/3132498
PMCID: PMC11018379
PMID: 38623557

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

Pub Med Non-Open Access

53. UK patient with multidrug-resistant tuberculosis.

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Kirby T.

DOI: 10.1016/S2213-2600(24)00109-7
PMID: 38608675

54. 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.

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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
PMID: 38488133 [Indexed for MEDLINE]

55. Treatment Outcome of Drug-Resistant Skeletal Tuberculosis: A Retrospective Analysis.

Indian J Orthop. 2024 Mar 2;58(4):402-411. doi: 10.1007/s43465-024-01110-w. eCollection 2024 Apr.

Gupta H(1), Arora R(1), Chadha M(1), Dhammi IK(1), Jain AK(1).

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BACKGROUND: Management outcomes of drug-resistant (DR) osteoarticular tuberculosis (OATB) is dismal as in pre-ATT era (1905). The studies documenting treatment outcome of DR-OATB are scarce; hence, present retrospective analysis was conducted to evaluate outcome of consecutive cases of DR-OATB.
METHODS: 45 consecutive patients of suspected DR-OATB were treated from 2010 onwards. Tissue samples were submitted for AFB smear, cytology/histology, liquid culture, CBNAAT/LPA besides gram's staining and aerobic/anaerobic culture. Patients were treated by individualized second-line ATT till documenting healed status by contrast MRI/PET. The changes in neurological deficit, deformities, and drug-induced adverse events were documented.
RESULTS: 37/45 patients, 15 males and 22 females, mean age 26.89 years were followed. DR was suspected observing poor clinico-radiological response/appearance of fresh lesions on ATT. All showed no growth on aerobic/anaerobic pyogenic culture. 29 (78%) had microbiologically proven drug

resistance and 8 (22%) were labeled as clinical drug resistance (CDR). 18/29 had multi-drug resistance. Mean prior ATT intake was 12.03 months 15 (40%) underwent surgical decompression. Mean duration of second-line ATT was 22.5 months (9-36 months). All patients achieved healed status with 8 (21%) developed side effects, most commonly hepatotoxicity, ototoxicity, and psychiatric disturbances. Average follow-up after completion of ATT was 40.5 months. CONCLUSION: We report a large series where patients of DR-OATB were suspected on clinical criteria, investigated by DST, and treated. Patients with proven drug resistance were treated by individualized second-line ATT. CDR cases were treated by MDR protocol. Genotypic DST (CBNAAT/LPA) improved demonstration of DR. We demonstrated healed status on MRI/PET with no recurrence at minimum 2-year follow-up.

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PMCID: PMC10963675
PMID: 38544531

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

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

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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.

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

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

Clin Infect Dis. 2024 Apr 10;78(4):1073. doi: 10.1093/cid/ciad594.

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PMID: 37930787 [Indexed for MEDLINE]

Conflict of interest statement: Potential conflicts of interest. The authors: No

reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

58. In silico identification of phytochemical inhibitors for multidrug-resistant tuberculosis based on novel pharmacophore generation and molecular dynamics simulation studies.

BMC Chem. 2024 Apr 18;18(1):77. doi: 10.1186/s13065-024-01182-7.

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BACKGROUND: Multidrug-resistant tuberculosis (particularly resistant to pyrazinoic acid) is a life-threatening chronic pulmonary disease. Running a marketed regime specifically targets the ribosomal protein subunit-1 (RpsA) and stops trans-translation in the non-mutant bacterium, responsible for the lysis of bacterial cells. However, in the strains of mutant bacteria, this regime has failed in curing TB and killing pathogens, which may only because of the ala438 deletion, which inhibit the binding of pyrazinoic acid to the RpsA active site. Therefore, such cases of tuberculosis need an immediate and effective regime.
OBJECTIVE: This study has tried to determine and design such chemotypes that are able to bind to the mutant RpsA protein.
METHODS: For these purposes, two phytochemical databases, i.e., NPASS and SANCDB, were virtually screened by a pharmacophore model using an online virtual screening server Pharmit.
RESULTS: The model of pharmacophore was developed using the potential inhibitor (zr115) for the mutant of RpsA. Pharmacophore-based virtual screening results into 154 hits from the NPASS database, and 22 hits from the SANCDB database. All the predicted hits were docked in the binding pocket of the mutant RpsA protein. Top-ranked five and two compounds were selected from the NPASS and SANCDB databases respectively. On the basis of binding energies and binding affinities of the compounds, three compounds were selected from the NPASS database and one from the SANCDB database. All compounds were found to be non-toxic and highly active against the mutant pathogen. To further validate the docking results and check the stability of hits, molecular dynamic simulation of three compounds were performed. The MD simulation results showed that all these finally selected compounds have stronger binding interactions, lesser deviation or fluctuations, with greater compactness compared to the reference compound.
CONCLUSION: These findings indicate that these compounds could be effective inhibitors for mutant RpsA.

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PMCID: PMC11027422
PMID: 38637835

Conflict of interest statement: The authors declare no competing interests

59. Global burden of MDR-TB and XDR-TB attributable to high fasting plasma glucose from 1990 to 2019: a retrospective analysis based on the global burden of disease study 2019.

Eur J Clin Microbiol Infect Dis. 2024 Apr;43(4):747-765. doi: 10.1007/s10096-024-04779-x. Epub 2024 Feb 17.

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PURPOSE: High fasting plasma glucose (HFPG) has been identified as a risk factor for drug-resistant tuberculosis incidence and mortality. However, the epidemic characteristics of HFPG-attributable multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) remain unclear. We aimed to analyze the global spatial patterns and temporal trends of HFPG-attributable MDR-TB and XDR-TB from 1990 to 2019.
METHODS: Utilizing data from the Global Burden of Disease 2019 project, annual deaths and disability-adjusted life years (DALYs) of HFPG-attributable MDR-TB and XDR-TB were conducted from 1990 to 2019. Joinpoint regression was employed to quantify trends over time.
RESULTS: From 1990 to 2019, the deaths and DALYs due to HFPG-attributable MDR-TB and XDR-TB globally showed an overall increasing trend, with a significant increase until 2003 to 2004, followed by a gradual decline or stability thereafter. The low sociodemographic index (SDI) region experienced the most significant increase over the past 30 years. Regionally, Sub-Saharan Africa, Central Asia and Oceania remained the highest burden. Furthermore, there was a sex and age disparity in the burden of HFPG-attributable MDR-TB and XDR-TB, with

young males in the 25-34 age group experiencing higher mortality, DALYs burden and a faster increasing trend than females. Interestingly, an increasing trend followed by a stable or decreasing pattern was observed in the ASMR and ASDR of HFPG-attributable MDR-TB and XDR-TB with SDI increasing.
CONCLUSION: The burden of HFPG-attributable MDR-TB and XDR-TB rose worldwide from 1990 to 2019. These findings emphasize the importance of routine bi-directional screening and integrated management for drug-resistant TB and diabetes.

DOI: 10.1007/s10096-024-04779-x
PMID: 38367094 [Indexed for MEDLINE]

60. An insight into the burden of drug-resistant tuberculosis in children.

Acta Paediatr. 2024 Apr;113(4):781-782. doi: 10.1111/apa.17120. Epub 2024 Jan 20.

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PMID: 38243684 [Indexed for MEDLINE]

61. Status of HIV and comorbidities in refugees with HIV from Ukraine.

HIV Med. 2024 Apr;25(4):479-483. doi: 10.1111/hiv.13597. Epub 2023 Dec 3.

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PURPOSE: To describe the clinical characteristics of refugees with HIV from Ukraine that seek continuation of medical care in Germany.
METHODS: Fourty-six refugees with HIV that had left Ukraine between 24 February and 30 December 2022 were examined. Information on patients' history was obtained using a standardized questionnaire for clinical care. Interviews were conducted in Russian during their first clinical presentation.
RESULTS: Fourty-six persons (41 females and 5 males) were included and their mean age was 39.6 (±8.4) years. The mean time since HIV diagnosis was 8.0 (median, IQR 7.15) years and 70.3% of participants currently received tenfofovir-DF, lamividine and dolutegravir. Most refugees had an undetectable HIV viral load and their current mean CD4 T cell count was 702 (SD ± 289) per µL. Serology revealed previous hepatitis B infection in 50.4% without evidence for replication, with undetectable anti-hepatitis B surface antigen in the remaining refugees. Antibodies against hepatitis C were present in 23 refugees (50%), but only 10 patients had been diagnosed with hepatitis C previously. Five refugees had undergone successful antiviral treatment for hepatitis C. Detectable HCV-RNA was evident in nine patients (19.6%). Sixteen (38.6%) refugees had a positive tuberculosis (TB) interferon gamma release assay, and four were on TB treatment for previously diagnosed infection. One had been diagnosed with multidrug-resistant (MDR) TB, two with pre-extensively drug-resistant (pre-XDR) TB and two with XDR TB and were treated with combinations of second-line and novel agents according to WHO guidelines.
CONCLUSIONS: Based on this preliminary analysis of a not fully representative cohort, refugees with HIV from Ukraine were young, mostly healthy females highly

adherent to antiretroviral therapy. The rate of transmittable co-infections urges early diagnostic evaluation and treatment.

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PMID: 38043508 [Indexed for MEDLINE]

62. Synthesis, antitubercular profile and molecular docking studies of quinazolinone-based pyridine derivatives against drug-resistant tuberculosis.

J Biomol Struct Dyn. 2024 Apr;42(7):3307-3317. doi: 10.1080/07391102.2023.2217928. Epub 2023 Jun 1.

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The promising quinazolinone-based pyridine derivatives (4a-j) were synthesized and subsequently tested for their antimycobacterial activities against the various drug-sensitive and drug-resistant Mycobacterium tuberculosis (Mtb) strains to combat infectious diseases and address growing concerns about the devastating effects of tuberculosis (TB). Utilizing 1H NMR, 13C NMR, and mass spectra, the structural and molecular confirmation of the synthesized compounds were deciphered. With minimum inhibitory concentration (MIC) values ranging from 0.31 to 19.13 µM, the results showed that compounds 4e and 4f showed promise anti-TB action against both drug-sensitive and drug-resistant TB strains. To study the cytotoxicity of synthesized molecules, normal Vero and mouse macrophage (RAW264.7) cell lines were utilized. Remarkably, it was revealed that at the highest concentration tested, none of the newly synthesized molecules were toxic to the Vero cell line. The binding patterns of the potent compounds 4b, 4e and 4f in the active site of the mycobacterial membrane protein Large 3

(MmpL3) protein are also revealed by molecular docking studies, which has contributed to the development of a structural rationale for Mtb inhibition. The physicochemical characteristics of the compounds were then predicted using theoretical calculations. Overall, the molecular docking results, physiochemical properties, and observed antimycobacterial activity all point to compound 4e with trifluoromethyl and compound 4f with nitro moiety as potential quinazolinone linked pyridine-based MmpL3 inhibitors.Communicated by Ramaswamy H. Sarma.

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PMID: 37261798 [Indexed for MEDLINE]

63. Automated Pulmonary Tuberculosis Severity Assessment on Chest X-rays.

J Imaging Inform Med. 2024 Apr 8. doi: 10.1007/s10278-024-01052-7. Online ahead of print.

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According to the 2022 World Health Organization's Global Tuberculosis (TB) report, an estimated 10.6 million people fell ill with TB, and 1.6 million died from the disease in 2021. In addition, 2021 saw a reversal of a decades-long trend of declining TB infections and deaths, with an estimated increase of 4.5% in the number of people who fell ill with TB compared to 2020, and an estimated yearly increase of 450,000 cases of drug resistant TB. Estimating the severity of pulmonary TB using frontal chest X-rays (CXR) can enable better resource allocation in resource constrained settings and monitoring of treatment response, enabling prompt treatment modifications if disease severity does not decrease over time. The Timika score is a clinically used TB severity score based on a CXR reading. This work proposes and evaluates three deep learning-based approaches for predicting the Timika score with varying levels of explainability. The first approach uses two deep learning-based models, one to explicitly detect lesion regions using YOLOV5n and another to predict the

presence of cavitation using DenseNet121, which are then utilized in score calculation. The second approach uses a DenseNet121-based regression model to directly predict the affected lung percentage and another to predict cavitation presence using a DenseNet121-based classification model. Finally, the third approach directly predicts the Timika score using a DenseNet121-based regression model. The best performance is achieved by the second approach with a mean absolute error of 13-14% and a Pearson correlation of 0.7-0.84 using three held-out datasets for evaluating generalization.

DOI: 10.1007/s10278-024-01052-7
PMID: 38587769

64. [Application and optimization of CRISPRi to the biology of Mycobacterium tuberculosis].

Zhonghua Jie He He Hu Xi Za Zhi. 2024 Apr 12;47(4):376-382. doi: 10.3760/cma.j.cn112147-20231019-00250.

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

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Tuberculosis, caused by infection with Mycobacterium tuberculosis (MTB), remains a global public health challenge. Multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) strains make tuberculosis more difficult to control. New tools to study the biology of MTB can identify novel targets for drug discovery. Recently, the Clustered Regularly Interspaced Short Palindromic Repeats interference (CRISPRi) combined with next-generation sequencing has provided many novel insights into the physiology and genetics of MTB. This review summarizes the application and optimization of CRISPRi in MTB biology.

Publisher:
结核分枝杆菌（MTB）感染导致的结核病仍然是全球公共卫生的巨大挑战。耐多药结核病（MDR-TB）和广泛耐药结核病（XDR-TB）菌株使得结核病治疗更加困难。不断研发新遗

传工具，探索MTB生理，有望发现新的药物靶点。其中，最近用于MTB研究的成簇规律间隔短回文重复序列干扰（CRISPRi）与高通量测序相结合，为揭示MTB生理和遗传提供了基础。本文综述了CRISPRi在MTB生物学研究中的应用及技术发展。.

DOI: 10.3760/cma.j.cn112147-20231019-00250
PMID: 38599816 [Indexed for MEDLINE]

65. Global Burden of Tuberculosis in Adolescents and Young Adults: 1990-2019.

Pediatrics. 2024 Apr 1;153(4):e2023063910. doi: 10.1542/peds.2023-063910.

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OBJECTIVE: Tuberculosis (TB) is a major health threat in adolescents and young adults. However, its burden in this population remains unclear. This study aimed to assess TB burden and changing trends in individuals aged 10 to 24 years from 1990 to 2019.
METHODS: All data were obtained from the Global Burden of Disease Study 2019. We calculated the percentage of relative changes in incident cases, deaths, and disability-adjusted life years (DALYs). The temporal trends of the incidence, mortality, and DALYs were assessed using estimated annual percentage changes (EAPCs).
RESULTS: At global level, TB incidence (per 100 000 population) decreased from 144.12 in 1990 to 97.56 in 2019, with average 1.28% (95% confidence interval [CI]: 1.36%-1.19%) of decline per year. Similar decreasing trends occurred across sex, age, sociodemographic index regions, and in most Global Burden of Disease study regions and countries. TB incidence in female adolescents decreased faster than that in male. However, there was an increasing trend in the incidence of extensively drug-resistant TB (EAPC = 11.23, 95% CI: 8.22-14.33) and multidrug-resistant TB without extensive drug resistance (EAPC = 3.28, 95% CI: 1.73-4.86). South Africa had the highest increase in TB incidence (EAPC = 3.51, 95% CI: 3.11-3.92).
CONCLUSIONS: Global TB incidence, mortality, and DALYs in adolescents and young adults decreased from 1990 to 2019. However, the incidence of drug-resistant TB increased. TB remains a threat in adolescents and young adults worldwide, especially in low- and middle-income countries.

DOI: 10.1542/peds.2023-063910
PMID: 38482587 [Indexed for MEDLINE]

66. T-wave morphology abnormalities in the STREAM stage 1 trial.

Expert Opin Drug Saf. 2024 Apr;23(4):469-476. doi: 10.1080/14740338.2024.2322116. Epub 2024 Mar 10.

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BACKGROUND: Shorter regimens for drug-resistant tuberculosis (DR-TB) have non-inferior efficacy compared with longer regimens, but QT prolongation is a concern. T-wave morphology abnormalities may be a predictor of QT prolongation.
RESEARCH DESIGN AND METHODS: STREAM Stage 1 was a randomized controlled trial in rifampicin-resistant TB, comparing short and long regimens. All participants had regular ECGs. QT/QTcF prolongation (≥500 ms or increase in ≥60 ms from baseline) was more common on the short regimen which contained high-dose moxifloxacin and clofazimine. Blinded ECGs were selected from the baseline, early (weeks 1-4), and late (weeks 12-36) time points. T-wave morphology was categorized as normal or abnormal (notched, asymmetric, flat-wave, flat peak, or broad). Differences between groups were assessed using Chi-Square tests (paired/unpaired, as appropriate).
RESULTS: Two-hundred participants with available ECGs at relevant times were analyzed (QT prolongation group n = 82; non-prolongation group n = 118). At baseline, 23% (45/200) of participants displayed abnormal T-waves, increasing to 45% (90/200, $p < 0.001$) at the late time point. Abnormalities were more common in participants allocated the Short regimen (75/117, 64%) than the Long (14/38, 36.8%, $p = 0.003$); these occurred prior to QT/QTcF ≥500 ms in 53% of the participants (Long 2/5; Short 14/25).
CONCLUSIONS: T-wave abnormalities may help identify patients at risk of QT prolongation on DR-TB treatment.

TRIAL REGISTRATION: The trial is registered at ClinicalTrials.gov (CT.gov identifier: NCT02409290). Current Controlled Trial number, ISRCTN78372190.

DOI: 10.1080/14740338.2024.2322116
PMID: 38462751 [Indexed for MEDLINE]

67. Estimated treatment costs for multidrug-resistant TB in the United States.

Int J Tuberc Lung Dis. 2024 Apr 1;28(4):214-215. doi: 10.5588/ijtld.23.0621.

Marks SM, Winston CA.

DOI: 10.5588/ijtld.23.0621
PMID: 38563338 [Indexed for MEDLINE]

68. The Effect of Immunoglobulin G on the Humoral Immunity in Patients with Tuberculosis/HIV Coinfection.

AIDS Res Hum Retroviruses. 2024 Apr;40(4):246-252. doi: 10.1089/AID.2023.0074. Epub 2024 Jan 31.

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Previously, an increase in clinical effectiveness of the antituberculosis treatment (ATT) and antiretroviral therapy (ART) in case of additional immunoglobulin G (IgG) administration in patients with multidrug-resistant tuberculosis (MDR-TB)/HIV coinfection was reported. The aim of this study was to investigate the impact of IgG administration in addition to the standard second-line ATT and ART on the humoral immunity status in patients with MDR-TB/HIV coinfection immune deficiency. The study involved 52 patients living with HIV with MDR-TB coinfection and CD4+ lymphocyte cell count below 50 cells/μCL. Patients in the control group and intervention group received the second-line ATT and ART; in addition, patients in the intervention group received IgG intravenously. The humoral immunity status was evaluated by measurement of IgA, IgE, IgG, and IgM in plasma. The standard ATT and ART

resulted in a two-step change in humoral immunity: IgM, IgG, IgA, and IgE levels gradually increased to a maximal level at the 5-month mark and started to gradually decrease after the 8-month mark. Addition of IgG to the standard therapy resulted in a steeper decrease in the immunoglobulin level in serum, especially IgG, compared with standard therapy alone, allowing for an earlier initiation of ART in patients in the intervention group.

DOI: 10.1089/AID.2023.0074
PMID: 38164121 [Indexed for MEDLINE]

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

Expert Rev Anti Infect Ther. 2024 Apr;22(4):219-227. doi: 10.1080/14787210.2023.2285917. Epub 2023 Nov 22.

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

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

DOI: 10.1080/14787210.2023.2285917
PMID: 37982155 [Indexed for MEDLINE]

70. Impact of Prior Tuberculosis Treatment With New/Companion Drugs on Clinical Outcomes in Patients Receiving Concomitant Bedaquiline and Delamanid for Multidrug- and Rifampicin-Resistant Tuberculosis.

Clin Infect Dis. 2024 Apr 10;78(4):1043-1052. doi: 10.1093/cid/ciad694.

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BACKGROUND: There are scarce data on the clinical outcomes of persons retreated with new/companion anti-tuberculosis (TB) drugs for multidrug- and rifampicin-resistant tuberculosis (MDR/RR-TB). We sought to evaluate the efficacy and safety of bedaquiline and delamanid containing regimens among patients with and without prior exposure to the new/companion drugs (bedaquiline, delamanid, linezolid, clofazimine, and fluoroquinolones).
METHODS: We conducted a retrospective cohort study among patients with pulmonary MDR/RR-TB in Georgia who received bedaquiline and delamanid combination as a part of a salvage regimen from November 2017 to December 2020 in a programmatic setting.
RESULTS: Among 106 persons with a median age of 39.5 years, 44 (41.5%) were previously treated with new/companion TB drugs. Patients with prior exposure to new/companion drugs had higher rates of baseline resistance compared to those without exposure to new/companion TB drugs (bedaquiline 15.2% vs 1.8%, linezolid 22.2% vs 16.7%). Sputum culture conversion rates among patients exposed and not exposed to new/companion drugs were 65.9% vs 98.0%, respectively (P < .001). Among patients with and without prior new/companion TB drug use, favorable

outcome rates were 41.0% and 82.3%, respectively (P < .001). Treatment adherence in 32 (30.2%) patients was ≤80%. Five of 21 patients (23.8%) who had a baseline and repeat susceptibility test had acquired bedaquiline resistance. QTC/F prolongation (>500 ms) was rare (2.8%).
CONCLUSIONS: Prior exposure to new/companion TB drugs was associated with poor clinical outcomes and acquired drug resistance. Tailoring the TB regimen to each patient's drug susceptibility test results and burden of disease and enhancing adherence support may improve outcomes.

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71. 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.

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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.

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72. [Annual progress of immunotherapy for tuberculosis in 2023].

Zhonghua Jie He He Hu Xi Za Zhi. 2024 Apr 12;47(4):371-375. doi: 10.3760/cma.j.cn112147-20231031-00283.

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

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As a chronic infectious disease, tuberculosis (TB) is closely related to immune regulation and immune effect. Immunotherapy which can improve the curative effect of tuberculosis and control the spread of tuberculosis, is one of the important means for the comprehensive treatment of tuberculosis. From October 2022 to September 2023, research on the immunotherapy of tuberculosis at home and abroad continues to increase, providing new opportunities for the treatment of multidrug-resistant and extensively drug-resistant tuberculosis.
Host-targeted therapy and therapeutic vaccines are new directions for research into TB adjuvant therapy.

Publisher:
结核病作为一种慢性感染性疾病，与免疫调控及免疫效应密切相关。免疫治疗作为结核病综合治疗的重要手段之一，可改善结核病的疗效、控制结核病的传播。2022年10月至2023年9月，国内外进行了多项关于结核病的免疫治疗研究，对耐多药、广泛耐药结核的治疗提供了新的可能。宿主靶向治疗及治疗性疫苗的研究是结核病辅助治疗探索的新方向。.

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PMID: 38599815 [Indexed for MEDLINE]

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

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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.

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PMID: 38615748

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

74. Computational investigation of phytochemicals identified from medicinal plant extracts against tuberculosis.

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Tuberculosis (TB) is still one of the world's most challenging infectious diseases and the emergence of drug-resistant Mycobacterium tuberculosis poses a significant threat to the treatment of TB. Identifying new medications based on local traditional remedies has become more essential. Gas Chromatography-Mass spectrometry (GC-MS) (Perkin-Elmer, MA, USA) was used to identify potential bioactive components in Solanum surattense, Piper longum, and Alpinia galanga plants sections. The fruits and rhizomes' chemical compositions were analyzed using solvents like petroleum ether, chloroform, ethyl acetate, and methanol. A total of 138 phytochemicals were identified, further categorized and finalized with 109 chemicals. The phytochemicals were docked with selected proteins (ethA, gyrB, and rpoB) using AutoDock Vina. The top complexes were selected and preceded with molecular dynamics simulation. It was found that the rpoB-sclareol complex is very stable, which means it could be further explored. The compounds were further studied for ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) properties. Sclareol has obeyed all the rules and it might be a potential chemical to treat TB.Communicated by Ramaswamy H. Sarma.

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75. Cryo-EM structures of Mycobacterium tuberculosis polynucleotide phosphorylase suggest a potential mechanism for its RNA substrate degradation.

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As one of the oldest infectious diseases in the world, tuberculosis (TB) is the second most deadly infectious disease after COVID-19. Tuberculosis is caused by Mycobacterium tuberculosis (Mtb), which can attack various organs of the human body. Up to now, drug-resistant TB continues to be a public health threat. Pyrazinamide (PZA) is regarded as a sterilizing drug in the treatment of TB due to its distinct ability to target Mtb persisters. Previously we demonstrated that a D67N mutation in Mycobacterium tuberculosis polynucleotide phosphorylase (MtbPNPase, Rv2783c) confers resistance to PZA and Rv2783c is a potential target for PZA, but the mechanism leading to PZA resistance remains unclear. To gain further insight into the MtbPNPase, we determined the cryo-EM structures of apo Rv2783c, its mutant form and its complex with RNA. Our studies revealed the Rv2783c structure at atomic resolution and identified its enzymatic functional groups essential for its phosphorylase activities. We also investigated the molecular mechanisms underlying the resistance to PZA conferred by the mutation. Our research findings provide structural and functional insights enabling the development of new anti-tuberculosis drugs.

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76. Indole Propionic Acid Disturbs the Normal Function of Tryptophanyl-tRNA Synthetase in Mycobacterium tuberculosis.

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Tuberculosis (TB) is the leading infectious disease caused by Mycobacterium tuberculosis and the second-most contagious killer after COVID-19. The emergence of drug-resistant TB has caused a great need to identify and develop new anti-TB drugs with novel targets. Indole propionic acid (IPA), a structural analog of tryptophan (Trp), is active against M. tuberculosis in vitro and in vivo. It has been verified that IPA exerts its antimicrobial effect by mimicking Trp as an allosteric inhibitor of TrpE, which is the first enzyme in the Trp synthesis pathway of M. tuberculosis. However, other Trp structural analogs, such as indolmycin, also target tryptophanyl-tRNA synthetase (TrpRS), which has two functions in bacteria: synthesis of tryptophanyl-AMP by catalyzing ATP + Trp and

producing Trp-tRNATrp by transferring Trp to tRNATrp. So, we speculate that IPA may also target TrpRS. In this study, we found that IPA can dock into the Trp binding pocket of M. tuberculosis TrpRS (TrpRSMtb), which was further confirmed by isothermal titration calorimetry (ITC) assay. The biochemical analysis proved that TrpRS can catalyze the reaction between IPA and ATP to generate pyrophosphate (PPi) without Trp as a substrate. Overexpression of wild-type trpS in M. tuberculosis increased the MIC of IPA to 32-fold, and knock-down trpS in Mycolicibacterium smegmatis made it more sensitive to IPA. The supplementation of Trp in the medium abrogated the inhibition of M. tuberculosis by IPA. We demonstrated that IPA can interfere with the function of TrpRS by mimicking Trp, thereby impeding protein synthesis and exerting its anti-TB effect.

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PMID: 38457660 [Indexed for MEDLINE]

77. GenoMycAnalyzer: a web-based tool for species and drug resistance prediction for Mycobacterium genomes.

BMC Genomics. 2024 Apr 20;25(1):387. doi: 10.1186/s12864-024-10320-3.

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BACKGROUND: Drug-resistant tuberculosis (TB) is a major threat to global public health. Whole-genome sequencing (WGS) is a useful tool for species identification and drug resistance prediction, and many clinical laboratories are transitioning to WGS as a routine diagnostic tool. However, user-friendly and high-confidence automated bioinformatics tools are needed to rapidly identify M. tuberculosis complex (MTBC) and non-tuberculous mycobacteria (NTM), detect drug resistance, and further guide treatment options.
RESULTS: We developed GenoMycAnalyzer, a web-based software that integrates functions for identifying MTBC and NTM species, lineage and spoligotype prediction, variant calling, annotation, drug-resistance determination, and data visualization. The accuracy of GenoMycAnalyzer for genotypic drug susceptibility testing (gDST) was evaluated using 5,473 MTBC isolates that underwent phenotypic DST (pDST). The GenoMycAnalyzer database was built to predict the gDST for 15 antituberculosis drugs using the World Health Organization mutational catalogue. Compared to pDST, the sensitivity of drug susceptibilities by the GenoMycAnalyzer for first-line drugs ranged from 95.9% for rifampicin (95% CI 94.8-96.7%) to 79.6% for pyrazinamide (95% CI 76.9-82.2%), whereas those for second-line drugs ranged from 98.2% for levofloxacin (95% CI 90.1-100.0%) to 74.9% for capreomycin (95% CI 69.3-80.0%). Notably, the integration of large deletions of the four resistance-conferring genes increased gDST sensitivity. The specificity of drug susceptibilities by the GenoMycAnalyzer ranged from 98.7% for amikacin (95% CI 97.8-99.3%) to 79.5% for ethionamide (95% CI 76.4-82.3%). The incorporated Kraken2 software identified 1,284 mycobacterial species with an accuracy of 98.8%. GenoMycAnalyzer also perfectly predicted lineages for 1,935 MTBC and spoligotypes for 54 MTBC.
CONCLUSIONS: GenoMycAnalyzer offers both web-based and graphical user interfaces, which can help biologists with limited access to high-performance computing systems or limited bioinformatics skills. By streamlining the interpretation of WGS data, the GenoMycAnalyzer has the potential to significantly impact TB management and contribute to global efforts to combat this infectious disease. GenoMycAnalyzer is available at http://www.mycochase.org .

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78. Bedaquiline, pretomanid, and linezolid in multidrug-resistant and

pre-extensively drug-resistant tuberculosis in refugees from Ukraine and Somalia in Germany.

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79. High-Dose Isoniazid Lacks EARLY Bactericidal Activity Against Isoniazid-resistant Tuberculosis Mediated by katG Mutations: A Randomized, Phase 2 Clinical Trial.

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Gausi K(1)(2), Ignatius EH(3), De Jager V(4), Upton C(5), Kim S(6), McKhann A(7), Moran L(8), Wiesner L(9), von Groote-Bidlingmaier F(10), Marzinek P(11), Vanker N(12), Yvetot J(13), Pierre S(14), Rosenkranz SL(15)(16), Swindells S(17), Diacon AH(18), Nuermberger EL(19), Denti P(20), Dooley KE(21); A5312 Study Team.

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RATIONALE: Observational studies suggest that high-dose isoniazid may be efficacious in treating multidrug-resistant tuberculosis (MDR-TB). However, its activity against Mycobacterium tuberculosis (M.tb) with katG mutations (which typically confer high-level resistance) is not established.
OBJECTIVE: To characterize early bactericidal activity (EBA) of high-dose isoniazid in patients with tuberculosis caused by katG-mutated M.tb.
METHODS: A5312 was a Phase 2A randomized, open-label trial. Participants with tuberculosis caused by katG-mutated M.tb were randomized to receive 15 or 20 mg/kg isoniazid daily for 7 days. Daily sputum samples were collected for quantitative culture. Intensive PK sampling was performed on day 6. Data were pooled across all A5312 participants for analysis (drug-sensitive, inhA-mutated, and katG-mutated M.tb). EBA was determined using nonlinear mixed-effects modelling.
RESULTS: Of 80 treated participants, 21 had katG-mutated M.tb. Isoniazid PK was best described by a two-compartment model with an effect of NAT2 acetylator phenotype on clearance. Model-derived Cmax and AUC in the 15 and 20 mg/kg groups were 15.0 and 22.1 mg/L and 57.6 and 76.8 mg·h/L, respectively. Isoniazid bacterial kill was described using an effect compartment and a sigmoidal Emax relationship. Isoniazid potency against katG-mutated M.tb was approximately 10-fold lower than against inhA-mutated M.tb. The highest dose (20 mg/kg) did

not demonstrate measurable EBA, except in a subset of slow NAT2 acetylators (who experienced the highest concentrations). There were no grade 3 or higher drug-related adverse events.
CONCLUSIONS: This study found negligible bactericidal activity of high-dose isoniazid (15-20 mg/kg) in the majority of participants with tuberculosis caused by katG-mutated M.tb. Clinical trial registration available at www. CLINICALTRIALS: gov, ID: NCT01936831.

DOI: 10.1164/rccm.202311-2004OC
PMID: 38564365

80. Multi-Drug Resistant Tuberculosis With Extensive Bilateral Lung Involvement Can be Cured With Just Three Drugs for 6 Months.

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[Article in English, Spanish]

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81. Mechanistic insights into the conformational changes and alterations in residual communications due to the mutations in the pncA Gene of Mycobacterium tuberculosis: A computational perspective for effective therapeutic solutions.

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Due to its emerging resistance to first-line anti-TB medications, tuberculosis (TB) is one of the most contagious illness in the world. According to reports, the effectiveness of treating TB is severely impacted by drug resistance, notably resistance caused by mutations in the pncA gene-encoded pyrazinamidase (PZase) to the front-line drug pyrazinamide (PZA). The present study focused on investigating the resistance mechanism caused by the mutations D12N, T47A, and H137R to better understand the structural and molecular events responsible for the resistance acquired by the pncA gene of Mycobacterium tuberculosis (MTB) at the structural level. Bioinformatics analysis predicted that all three mutations were deleterious and located near the active centre of the pncA, affecting its functional activity. Furthermore, molecular dynamics simulation (MDS) results established that mutations significantly reduced the structural stability and caused the rearrangement of FE2+ in the active centre of pncA. Moreover, essential dynamics analysis, including principal component analysis (PCA) and free energy landscape (FEL), concluded variations in the protein motion and decreased conformational space in the mutants. Additionally, the mutations potentially impacted the network topologies and altered the residual communications in the network. The complex simulation study results established the significant movement of the flap region from the active centre of mutant complexes, further supporting the flap region's significance in developing resistance to the PZA drug. This study advances our knowledge of the primary cause of the mechanism of PZA resistance and the structural dynamics of pncA mutants, which will help us to design new and potent chemical scaffolds to treat drug-resistant TB (DR-TB).

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82. Emerging insight of whole genome sequencing coupled with protein structure prediction into the pyrazinamide-resistance signature of Mycobacterium tuberculosis.

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Pyrazinamide (PZA) is considered to be a pivotal drug to shorten the treatment of both drug-susceptible and drug-resistant tuberculosis, but its use is challenged by the reliability of drug-susceptibility testing (DST). PZA resistance in Mycobacterium tuberculosis (MTB) is relevant to the amino acid substitution of pyrazinamidase that is responsible for the conversion of PZA to active pyrazinoic acid (POA). The single nucleotide variants (SNVs) within ribosomal protein S1 (rpsA) or aspartate decarboxylase (panD), the binding targets of POA, has been reported to drive the PZA-resistance signature of MTB. In this study, whole genome sequencing (WGS) was used to identify SNVs within the pncA, rpsA and panD genes in 100 clinical MTB isolates associated with DST results for PZA. The potential influence of high-confidence, interim-confidence or emerging variants on the interplay between target genes and PZA or POA was simulated computationally, and predicted with a protein structure modelling approach. The DST results showed weak agreement with the identification of high-confidence variants within the pncA gene (Cohen's kappa coefficient=0.58), the analytic results of WGS coupled with protein structure modelling on pncA mutants (Cohen's kappa coefficient=0.524) or related genes (Cohen's kappa coefficient=0.504). Taken together, these results suggest the practicable application of a genotypic-coupled bioinformatic approach to manage PZA-containing regimens for patients with MTB.

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83. 4-(Benzyloxy)phenol-induced p53 exhibits antimycobacterial response triggering phagosome-lysosome fusion through ROS-dependent intracellular Ca(2+) pathway in THP-1 cells.

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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.

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