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1. Pyrazinamide Resistance: A Major Cause of Switching Shorter to Longer Bedaquiline-based Regimens in Multidrug-resistant Tuberculosis Patients.

Int J Mycobacteriol. 2024 Oct 1;13(4):430-435. doi: 10.4103/ijmy.ijmy_164_24. Epub 2024 Dec 19.

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BACKGROUND: All-oral regimens, including bedaquiline, are now standard in shorter treatment regimens (STRs) for multidrug-resistant tuberculosis (MDR-TB). Resistance or intolerance to drugs in STR often necessitates a switch to longer treatment regimens (LTRs). This study aims to identify the factors associated with this transition in MDR-TB patients.
METHODS: We conducted a retrospective analysis of medical records from MDR-TB patients treated with STR at Haji Hospital, Surabaya, between January 2022 and January 2023. Data on drug-resistance profiles, determined by drug-susceptibility testing (DST), and line probe assay, as well as adverse effects, were collected.
RESULTS: Among 20 eligible patients, 8 (40.0%) switched from STR to LTR within the first 4 months. Resistance was observed in 62.5% of these patients for pyrazinamide, 25.0% for high-dose isoniazid, and 12.5% for levofloxacin. The overall prevalence of pyrazinamide resistance was 25.0%. A history of prior antitubercular treatment was significantly associated with pyrazinamide resistance (P = 0.015; RR - 16.000; confidence interval 95% 1.274-200.917).
CONCLUSION: Pyrazinamide resistance is a major factor for switching from STR to LTR in MDR-TB patients, particularly among those with previous TB treatment. Rapid DST for pyrazinamide is essential for the early identification of resistance and timely adjustments to treatment regimens.

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PMID: 39700165 [Indexed for MEDLINE]

2. Navigating Extrapulmonary Tuberculosis: A Case Series from a Tertiary Care Facility Highlighting Rare Presentations, Diagnostic Challenges, Drug

Resistance, and Therapeutic Complexities.

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BACKGROUND: Extrapulmonary tuberculosis (EP-TB) constitutes one-fifth of all tuberculosis (TB) cases. EP-TB mimics common infections which pose diagnostic dilemma, requires extensive diagnostics that culminate into therapeutic delay often resulting in irrational and empirical institution of antitubercular therapy (ATT) in challenging cases. This supplemented by poor treatment compliance resulted in emergence of Drug-resistant (DR) strains of EP-TB which further impedes the path to recovery. The aim of the present series is to study the rare and diverse presentations of EP-TB caused by drug-sensitive (DS) and DR mycobacterium that require a multi-modal diagnostic approach and appropriate treatment.
METHODS: This observational retrospective series incorporated six rare EP-TB cases, excluding those with solitary lung affection and underwent comprehensive diagnostic tests aimed at microbial isolation from affected tissues with subsequent drug resistance testing. They were treated by integrative approach, standard (first/second/third line) ATT while few required emergent surgical interventions. Patient outcomes were evaluated based on clinicoradiological improvement and microbiological clearance determined in follow-up.
RESULTS: Out of six cases (four males and two females; age range: 14-62 years), pleural linings, kidneys, brain and its lining, skin, and axial skeleton were directly affected, while superior mesenteric artery (SMA) syndrome was an indirect consequence of infection. Elective thoracic and urosurgical interventions supplemented medical management in two cases while urgent neurosurgical decompression improved outcomes in Pott's spine case that exhibited drug resistance. Notably of five DS EP-TB, one patient showed poor clinical response necessitating treatment escalation while nutritional rehabilitation was key in SMA syndrome.
CONCLUSIONS: EP-TB requires high clinical suspicion and a multidisciplinary approach for diagnosis and treatment. Addressing treatment adherence, with emphasis on good nutrition to tackle cachexia, is necessary for favorable outcomes.

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3. Effect of COVID-19 restriction measures on multidrug resistant tuberculosis case notifications and treatment outcomes at treatment centres in Uganda.

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BACKGROUND: Multidrug resistant tuberculosis (MDR-TB) is a global public health threat. In 2021, an incidence of 3.6% was reported among new TB patients, and 18% was reported among previously treated patients. The emergence of the COVID-19 pandemic impacted the health sector, although little is known about the effect of restrictive COVID-19 measures on MDR-TB case notifications and treatment outcomes in Uganda. This study aimed to assess the effect of COVID-19 restriction measures on MDR-TB case notifications and treatment outcomes at treatment centres in Uganda.
METHODS: This was a retrospective cohort study in which a total of 483 participants were enrolled-238 before (March 2018-February 2020) and 245 during (March 2020-February 2022) COVID-19 restrictions. The data were extracted from the Drug-Resistant Tuberculosis (DR-TB) Health Management Information System (HMIS), and patient charts, and census sampling was employed. Interrupted time series (ITSA) was used to compare MDR-TB case notifications and treatment outcomes.
RESULTS: Before the COVID-19 restrictions, the majority 58.0% were aged less than or equal to 38 years whereas during the restrictions, the majority 51.8% were aged greater than 38 years. A total of 238 cases of MDRTB were reported

before, and 245 cases were reported during the restrictions. There was no immediate (β2; 0.134) or sustained (β3; 0.494) impact of COVID-19 restriction measures on monthly MDR-TB case notifications. The mean number of monthly MDR-TB notifications was similar for the 3-month period before (11.0 cases per month) and during (10.0 cases per month) the COVID-19 restrictions (p-value 0.661). The proportions of patients who achieved successful MDR-TB treatment before (81.5%) and during (81.7%) COVID-19 restriction was not significantly different (p-value < 0.001). During the COVID-19 restrictions, not being married (aPR 0.85, 95% CI: 0.74-0.97) and treatment delay greater than 7 days (aPR 0.87, 95% CI 0.78-0.96) were negatively associated with successful treatment outcomes. CONCLUSION: Restrictive COVID-19 measures did not affect MDR-TB case notifications or treatment outcomes. Not being married and having a treatment delay greater than 7 days reduced the chances of a successful treatment outcome during COVID-19. The WHO and MoH should continue strengthening active case finding, contact screening and community engagement to consolidate MDR-TB control and management in preparation for similar future pandemics.

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Conflict of interest statement: Declarations. Ethical approval: was obtained from the Makerere University School of Medicine Research Ethics Committee (SOMREC (Mak-SOMREC-2022-378)). Administrative clearance was sought from the Ministry of Health, National TB and Leprosy Program and the heads of health facilities where the study was conducted. A waiver of informed consent was obtained from the SOMREC for the use of existing health facility records whose owners were not available at the time of data collection. The data were kept confidential, and unique identification numbers were assigned to the participants. Consent for publication: Not applicable. Competing interests: The authors declare no competing interests.

4. TB treatment delays and associated risk factors in Dushanbe, Tajikistan, 2019-2021.

BMC Infect Dis. 2024 Dec 18;24(1):1398. doi: 10.1186/s12879-024-10265-8.

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BACKGROUND: In Tajikistan, where there are about 8,000 cases annually, many new cases are being diagnosed with severe disease, indicating a delay in receiving care. We aimed to estimate the proportion with delayed care and the main factors contributing to delayed care.
METHODS: Using a retrospective cohort design, we conducted a study that included all people aged over 15 years who were newly diagnosed with pulmonary TB in Dushanbe from 2019 to 2021. We defined 'patient delay' as > 14 days from TB symptom onset to the first provider visit and 'provider delay' as > 3 days from the first visit to treatment initiation. Data was abstracted from medical records and participants were interviewed in-person. Multivariable negative binomial regression was used to estimate adjusted risk ratios (aRR) and 95% confidence intervals (CI).
RESULTS: Of 472 participants, 49% were male, 65% had lung tissue cavitation, 33% had drug resistant TB, 11% had diabetes, 4% had HIV, and. Reported cases dropped from 196 in 2019 to 109 in 2020 and increased to 167 in 2021. The proportion of people experiencing patient delays was 82%, 72%, and 90% per year, respectively. The proportion of provider delays was 44%, 41% and 29% per year. Patient delay was associated with year (aRR: 1.09 [CI:1.02-1.18] in 2021 vs. 2019), age (aRR:0.91 [0.82-0.99] for 40-59-year-olds vs. 15-39-year-olds), having HIV (aRR:1.22 [1.08-1.38]), having blood in sputum (aRR:1.19 [1.10-1.28]), chest pain (aRR:1.32 [1.14-1.54]), having at least two structural barriers vs. none (aRR:1.52 [1.28-1.80]), having one of the following barriers: long wait lines (aRR:1.36 [1.03-1.80]), feeling that healthcare services were expensive (aRR:1.54 [1.28-1.85]), or having no time or too much work (aRR:1.54 [1.29-1.84]). Provider delay was associated with year (aRR: 0.67 [0.51-0.89] in 2021 vs. 2019), patients having to pay for X-ray services (aRR: 1.59 [1.22-2.07]) and lacking direct-observed-therapy (DOTS) in facility (aRR: 1.61 [1.03-2.52]).
CONCLUSIONS: Patient delay was high before the COVID-19 pandemic and increased in 2021, while provider delay decreased during this time. Addressing structural barriers to healthcare services, such as increased DOTS facilities, expanded hours, and zero fees, may decrease delays.

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Conflict of interest statement: Declarations. Ethics approval and consent to participate: Our study was conducted in accordance the Declaration of Helsinki. Ethical approval for the study was received from the local ethical commission of the Asfendiyarov Kazakh National Medical University, Kazakhstan (No. 6 (129), 05/25/2022) and the Ministry of Health of Tajikistan. This activity was reviewed by the CDC and was determined to be non-research and conducted consistently with applicable U.S. federal law and CDC policy (45 C.F.R. part 46, 21 C.F.R. part 56; 42 U.S.C. 241(d); 5 U.S.C. § 552a; 44 U.S.C. 3501 et seq.). Clinical trial number: not applicable. Informed consent was obtained from all participants, oral consent was obtained for participants interviewed virtually and written consent for those interviewed in-person. Written informed consent was obtained from parents of participants ages 15–17 years old who also provided verbal assent for participation. Consent for publication: Not applicable. Competing interests: The authors declare no competing interests. The findings and conclusions in this report are those of the author(s) and do not necessarily represent the official position of the U.S. Centers for Disease Control and Prevention.

5. Genotypes and drug resistance pattern of Mycobacterium tuberculosis complex among clinically diagnosed pulmonary tuberculosis patients.

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BACKGROUND: Clinically diagnosed pulmonary tuberculosis (TB) (CDPTB) patients account for a huge proportion of TB. However, little is known about the genetic diversity and drug resistance profile of Mycobacterium tuberculosis Complex

(MTBC) strains in this group of patients.
METHOD: Unmatched case-control study was conducted among 313 PTB patients to compare the genetic diversity of MTBC and their drug resistance profiles among CDPTB (n = 173) and bacteriologically confirmed pulmonary TB (BCPTB) (n = 140) patients. Lowenstein-Jensen (LJ) culture, geneXpert and acid fast staining were performed on sputum specimen collected from both CDPTB and BCPTB patients. Spoligotyping, whole genome sequencing (WGS) and phenotypic drug resistance testing (DST) were done for a subset of LJ grown MTBC isolates. Data was analyzed by STATA version 17 software and a p-value <0.05 were considered statistically significant.
RESULTS: The proportion of lineage 3 was larger among CDPTB patients (31%, 13/42) compared to BCPTB patients (15%, 11/74) (p-value <0.05). A higher proportion of MTBC isolates from CDPTB 16.6% (3/18) were phenotypically resistant to one or more anti-TB drugs than BCPTB 12% (4/33) (p-value >0.05). A single lineage 3 strain resistant to all the primary anti-TB drugs was detected in one CDPTB by both DST methods.
CONCLUSION: The observed differences in the genotypes of MTBC isolates between CDPTB and BCPTB patients may be attributed to challenges in the identification of CDPTB that requires further investigation on sequenced genome of the MTBC strains for better understanding and recommendation based on the current finding. There was also primary drug resistant TB among culture positive CDPTB patients which would be otherwise missed by current national protocols.

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

6. Sodium, Potassium-Adenosine Triphosphatase as a Potential Target of the Anti-Tuberculosis Agents, Clofazimine and Bedaquiline.

Int J Mol Sci. 2024 Dec 4;25(23):13022. doi: 10.3390/ijms252313022.

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Multidrug-resistant tuberculosis (MDR-TB) patients are treated with a standardised, short World Health Organization (WHO) regimen which includes clofazimine (CFZ) and bedaquiline (BDQ) antibiotics. These two antibiotics lead to the development of QT prolongation in patients, inhibiting potassium (K+) uptake by targeting the voltage-gated K+ (Kv)11.1 (hERG) channel of the cardiomyocytes (CMs). However, the involvement of these antibiotics to regulate other K+ transporters of the CMs, as potential mechanisms of QT prolongation, has not been explored. This study determined the effects of CFZ and BDQ on sodium, potassium-adenosine triphosphatase (Na+,K+-ATPase) activity of CMs using rat cardiomyocytes (RCMs). These cells were treated with varying concentrations of CFZ and BDQ individually and in combination (1.25-5 mg/L). Thereafter, Na+,K+-ATPase activity was determined, followed by intracellular adenosine triphosphate (ATP) quantification and cellular viability determination. Furthermore, molecular docking of antibiotics with Na+,K+-ATPase was determined. Both antibiotics demonstrated dose-response inhibition of Na+,K+-ATPase activity of the RCMs. The greatest inhibition was demonstrated by combinations of CFZ and BDQ, followed by BDQ alone and, lastly, CFZ. Neither antibiotic, either individually or in combination, demonstrated cytotoxicity. Molecular docking revealed an interaction of both antibiotics with Na+,K+-ATPase, with BDQ showing higher protein-binding affinity than CFZ. The inhibitory effects of CFZ and BDQ, individually and in combination, on the activity of Na+,K+-ATPase pump of the RCMs highlight the existence of additional mechanisms of QT prolongation by these antibiotics.

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

7. Therapeutic Strategies for Tuberculosis: Progress and Lessons Learned.

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Tuberculosis (TB) remains a significant global health challenge, ranking second only to COVID-19 as the leading cause of death from a single infectious agent, with 1.3 million TB-related deaths reported in 2022. Treatment efficacy has been compromised by the emergence of drug-resistant strains, including rifampin-resistant TB (RR-TB), multidrug-resistant TB (MDR-TB), and extensively drug-resistant TB (XDR-TB). Although first-line drugs like isoniazid, rifampicin, pyrazinamide, and ethambutol form the cornerstone of TB therapy, the rise of resistant strains necessitates the use of second-line drugs, which often come with increased toxicity and limited accessibility. Recent advances have focused on repurposing existing compounds and developing new drugs with novel mechanisms of action. Promising agents such as second-generation bedaquiline analogs (TBAJ-587, TBAJ-876), sudapyridine (WX-081), delamanid, pretomanid, and TBI-166 (pyrifazimine) have shown efficacy against resistant Mtb strains. Innovative treatment regimens like the BPaLM protocol-combining bedaquiline, pretomanid, linezolid, and moxifloxacin-offer shorter, all-oral therapies with higher cure rates. Personalized treatment durations and dose optimizations are becoming feasible through risk stratification algorithms and pharmacokinetic/pharmacodynamic studies. Immunotherapy is emerging as a complementary strategy to enhance the host's immune response against Mtb. Agents such as vitamin D, corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), statins, metformin, and biological agents like interleukins and granulocyte-macrophage colony-stimulating factor are under exploration. Additionally, cell therapies involving mesenchymal stem cells and immune effector cells present new therapeutic avenues. Despite these advancements, significant challenges remain in achieving the World Health Organization's "End TB Strategy" goals, particularly as the COVID-19 pandemic has diverted resources and attention. Ongoing research and global collaboration are crucial to develop novel therapeutic strategies, optimize treatment regimens, and ultimately reduce

the global burden of TB.

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8. Cost of TB care and equity in distribution of catastrophic TB care costs across income quintiles in India.

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BACKGROUND: Tuberculosis (TB) poses a significant social and economic burden to households of persons with TB (PwTB). Despite free diagnosis and care under the National TB Elimination Programme (NTEP), individuals often experience significant out-of-pocket expenditure and lost productivity, causing financial catastrophe. We estimated the costs incurred by the PwTB during TB care and identified the factors associated with the costs.
METHODS: In our cross-sectional study, we used multi-stage sampling to select PwTB notified under the NTEP, whose treatment outcome was declared between May 2022 and February 2023. Total patient costs were measured through direct medical, non-medical and indirect costs. Catastrophic costs were defined as expenditure on TB care > 20% of the annual household income. We determined the factors influencing the total cost of TB care using median regression. We plotted concentration curves to depict the equity in distribution of catastrophic costs across income quintiles. We used a cluster-adjusted, generalized model to determine the factors associated with catastrophic costs.
RESULTS: The mean (SD) age of the 1407 PwTB interviewed was 40.8 (16.8) years. Among them, 865 (61.5%) were male, and 786 (55.9%) were economically active. Thirty-four (2.4%) had Drug Resistant TB (DRTB), and 258 (18.3%) had been hospitalized for TB. The median (Interquartile range [IQR] and 95% confidence interval [CI]) of total costs of TB care was US$386.1 (130.8, 876.9). Direct

costs accounted for 34% of the total costs, with a median of US$78.4 (43.3, 153.6), while indirect costs had a median of US$279.8 (18.9,699.4). PwTB < 60 years of age (US$446.1; 370.4, 521.8), without health insurance (US$464.2; 386.7, 541.6), and those hospitalized(US$900.4; 700.2, 1100.6) for TB experienced higher median costs. Catastrophic costs, experienced by 45% of PwTB, followed a pro-poor distribution. Hospitalized PwTB (adjusted prevalence ratio [aPR] = 1.9; 1.6, 2.2) and those notified from the private sector (aPR = 1.4; 1.1, 1.8) were more likely to incur catastrophic costs.
CONCLUSIONS: PwTB in India incur high costs mainly due to lost productivity and hospitalization. Nearly half of them experience catastrophic costs, especially those from poorer economic quintiles. Enabling early notification of TB, expanding the coverage of health insurance schemes to include PwTB, and implementing TB sensitive strategies to address social determinants of TB may significantly reduce catastrophic costs incurred by PwTB.

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Conflict of interest statement: Declarations. Ethics approval and consent to participate: The Institutional Human Ethics Committee (IHEC) of Indian Council of Medical Research-National Institute of Epidemiology (ICMR-NIE) (NIE/IHEC/202201–13) approved the study. A non-disclosure agreement was signed between ICMR-NIE and the Central TB Division for sharing of Ni-kshay data. We obtained informed written consent from all the study participants or family members (in case of deceased PwTB) after sharing the participant information sheet in the regional language and this process was approved by the ethics committee. Consent for publication: Not applicable. Competing interests: The authors declare that they have no competing interests.

9. Machine learning-based prediction of antibiotic resistance in Mycobacterium tuberculosis clinical isolates from Uganda.

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BACKGROUND: Efforts toward tuberculosis management and control are challenged by the emergence of Mycobacterium tuberculosis (MTB) resistance to existing anti-TB drugs. This study aimed to explore the potential of machine learning algorithms in predicting drug resistance of four anti-TB drugs (rifampicin, isoniazid, streptomycin, and ethambutol) in MTB using whole-genome sequence and clinical data from Uganda. We also assessed the model's generalizability on another dataset from South Africa.
RESULTS: We trained ten machine learning algorithms on a dataset comprising of 182 MTB isolates with clinical data variables (age, sex, HIV status) and SNP mutations across the entire genome as predictor variables and phenotypic drug-susceptibility data for the four drugs as the outcome variable. Model performance varied across the four anti-TB drugs after a five-fold cross validation. The best model was selected considering the highest Mathews Correlation Coefficient (MCC) and Area Under the Receiver Operating Characteristic Curve (AUC) score as key metrics. The Logistic regression excelled in predicting rifampicin resistance (MCC: 0.83 (95% confidence intervals (CI) 0.73-0.86) and AUC: 0.96 (95% CI 0.95-0.98) and streptomycin (MCC: 0.44 (95% CI 0.27-0.58) and AUC: 0.80 (95% CI 0.74-0.82), Extreme Gradient Boosting (XGBoost) for ethambutol (MCC: 0.65 (95% CI 0.54-0.74) and AUC: 0.90 (95% CI 0.83-0.96) and Gradient Boosting (GBC) for isoniazid (MCC: 0.69 (95% CI 0.61-0.78) and AUC: 0.91 (95% CI 0.88-0.96). The best performing model per drug was only trained on the SNP dataset after excluding the clinical data variables because intergrating them with SNP mutations showed a marginal improvement in the model's performance. Despite the high MCC (0.18 to 0.72) and AUC (0.66 to 0.95) scores for all the best models with the Uganda test dataset, LR model for rifampicin and streptomycin didn't generalize with the South Africa dataset compared to the GBC and XGBoost models. Compared to TB profiler, LR for RIF was very sensitive and the GBC for INH and XGBoost for EMB were very specific on the Uganda dataset. TB profiler outperformed all the best models on the South Africa dataset. We identified key mutations associated with drug resistance for these antibiotics. HIV status was also identified among the top significant features in predicting drug resistance.
CONCLUSION: Leveraging machine learning applications in predicting antimicrobial resistance represents a promising avenue in addressing the global health challenge posed by antimicrobial resistance. This work demonstrates that integration of diverse data types such as genomic and clinical data could improve resistance predictions while using machine learning algorithms, support

robust surveillance systems and also inform targeted interventions to curb the rising threat of antimicrobial resistance.

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10. Understanding tuberculosis transmission and progression: A prospective cohort study of index cases and close contacts in Moldova.

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OBJECTIVES: This study aims to determine the progression rate, risk factors and timeline for the progression from exposure to active tuberculosis (TB) in a high-risk population. Using a prospective cohort in the Republic of Moldova, we investigated pulmonary TB disease progression among close contacts of patients with TB in a low-burden country with high rates of drug-resistant TB.
METHODS: Close contacts of patients with newly diagnosed TB were recruited and monitored to evaluate for progression rates to active TB. Data collected

included demographic information, medical and exposure history, and clinical samples. Follow-up clinical evaluations of close contacts were conducted at regular intervals over at least 24 months to monitor for progression to TB disease.
RESULTS: The overall incidence rate of TB disease among close contacts was 3.7%. Among the close contacts, 2.3% were identified as progressor cases, developing TB disease more than 30 days after index case treatment initiation. Thirteen (1.3%) were co-prevalent cases, diagnosed within 30 days of index case treatment initiation. Identified risk factors for progression included male sex, active tobacco use, prior TB infection, and frequent, prolonged exposure to index cases. Close contacts with daily exposure of more than eight hours had a significantly higher risk of disease progression (adjusted OR: 4.28, 95% CI: 1.79-10.23).
CONCLUSION: The incidence of TB disease among close contacts was consistent with global findings, highlighting the need for enhanced diagnostic tools and targeted interventions to manage TB transmission and progression. These results underscore the importance of contact tracing and progression monitoring in low-burden, high drug-resistant TB settings. Future research should focus on developing a better understanding of factors contributing to the risk for and timeline of TB disease progression, and more precise methods, including biomarkers, to identify individuals at the highest risk for progression from TB exposure to active disease.

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11. Enhanced Rapid Screening for Multidrug-resistant tuberculosis through combined cardiometabolic and inflammatory indices: a cross-sectional study.

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Multidrug-resistant tuberculosis (MDR-TB) remains a global public health challenge. We aimed to investigate the utility of combining the cardiometabolic index (CMI) and systemic inflammation response index (SIRI) as biomarkers for rapid MDR-TB screening. Data were collected from 2,620 TB patients in Zibo city from 2018 to 2021. Logistic regression and receiver operating characteristic (ROC) curve analyses were used to evaluate the associations and diagnostic performance of CMI and SIRI with MDR-TB. The prevalence of MDR-TB was 5.0% in new TB patients and 20.5% in recurrent TB patients. Both CMI and SIRI were significantly associated with MDR-TB in all models ($P < 0.05$). In new TB patients, the area under the curve (AUC) values of the ROC curves for SIRI, CMI, and their combination were 0.845, 0.806, and 0.910, respectively. In recurrent TB patients, the AUC values were 0.730, 0.875, and 0.902, respectively. The optimal cut-off points for SIRI and CMI were 0.72 and 1.81 in new TB patients, and 1.05 and 1.48 in recurrent TB patients, respectively. In conclusion, combining CMI and SIRI shows promise as a low-invasive, cost-effective tool for early MDR-TB screening, warranting further validation in diverse populations and TB subtypes.

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Conflict of interest statement: Declarations. Ethics approval and consent to participate: This study was approved by the Ethics Committee of Zibo First Hospital, and signed informed consent forms were obtained from all participants. Competing interests: The authors declare no competing interests.

12. Efficacy and Safety of Combined Bedaquiline and Delamanid Use among Patients with Multidrug-Resistant Tuberculosis in Beijing, China.

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OBJECTIVES: The combined use of bedaquiline and delamanid (BDQ-DLM) is limited by an increased risk of prolonging the QTc interval. We retrospectively evaluated patients who received DLM/BDQ-containing regimens at a TB-specialized hospital. We aimed to present clinical efficacy and safety data for Chinese patients.
METHODS: This case-control study included patients with multidrug-resistant tuberculosis (MDR-TB) treated with BDQ alone or BDQ plus DLM.
RESULTS: A total of 96 patients were included in this analysis: 64 in the BDQ group and 32 in the BDQ + DLM group. Among the 96 patients with positive sputum culture at the initiation of BDQ alone or BDQ combined with DLM, 46 patients (71.9%) in the BDQ group and 29 (90.6%) in the BDQ-DLM group achieved sputum culture conversion during treatment. The rate of sputum culture conversion did not differ between the two groups. The time to sputum culture conversion was significantly shorter in the BDQ-DLM group than in the BDQ group. The most frequent adverse event was QTc interval prolongation; however, the frequency of adverse events did not differ between the groups.
CONCLUSION: In conclusion, our results demonstrate that the combined use of BDQ and DLM is efficacious and tolerable in Chinese patients infected with MDR-TB. Patients in the BDQ-DLM group achieved sputum culture conversion sooner than those in the BDQ group.

DOI: 10.3967/bes2024.088
PMID: 39622668 [Indexed for MEDLINE]

13. Prevalence, patterns, and determinants of drug-resistant tuberculosis in Gulf Cooperation Council countries: an updated systematic review.

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Drug resistance (DR) to antituberculosis drugs is a growing global problem that threatens the successful control of tuberculosis (TB) globally and within the Gulf Cooperation Council (GCC). In the GCC, TB remains a major public health issue. Understanding the prevalence and patterns of drug resistance to antituberculosis drugs is crucial for developing effective prevention and treatment strategies. Hence, the present systematic review is aimed at assessing the prevalence, pattern, and risk factors of drug-resistant TB (DR-TB) in GCC countries. We conducted this systematic review adhering to the guidelines outlined in the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 Statement. Using the relevant keywords in the major databases, we included peer-reviewed articles that were published from 01 January 2014 and onwards in English language journals. The prevalence and patterns of DR-TB levels in different countries were different. Isoniazid monoresistance was the most commonly found type of resistance, with varying degrees of prevalence of multidrug-resistant tuberculosis (MDR-TB). Risk factors for DR-TB included diabetes mellitus, past TB treatment, younger age, female gender, and renal failure. There was a positive correlation between expatriate status and DR-TB. Collaborative actions by relevant stakeholders are essential to implement evidence-based interventions that reduce the DR-TB burden and improve overall community health. Ongoing research and surveillance activities are necessary for monitoring patterns, identifying new risk factors, and providing focused interventions to lessen the threat of DR-TB on public health in GCC countries.

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PMID: 39619190 [Indexed for MEDLINE]

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

14. Revealing disparities in representation in knowledge generation and guideline

development.

BMC Health Serv Res. 2024 Nov 30;24(1):1516. doi: 10.1186/s12913-024-11958-1.

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BACKGROUND: Multidrug-resistant tuberculosis (MDR/RR-TB) is a major global health challenge, disproportionately affecting low- and lower-middle-income countries (LLMICs). The World Health Organization (WHO) generates guidance to address the problem. Here, we explore the extent to which guidance and related knowledge are generated by experts living in the most-affected countries and consider the results in the context of the movement to decolonize global health.
METHODS: We examined the composition of World Health Organization (WHO) MDR/RR-TB treatment Guideline Development Groups (GDGs) from 2016 to 2022. We classified GDG members according to the MDR/RR-TB burden and World Bank income level of the country of their institutional affiliation. We also searched PubMed to identify peer-reviewed publications from 2016 to 2023 which emanated from individual-patient-data meta-analysis like those done for Guideline review, and classified the publication authors according to the same indicators.
RESULTS: There were 33 high-burden MDR/RR-TB countries during the time period. Of these, 72.1% were LLMICs and none was high-income. In contrast, only 30.3% of WHO GDG members and 10.4% of peer-reviewed publication authors were from LLMICs. Representatives from high-MDR/RR-TB-burden countries comprised 34.3% of WHO GDG members and 14.7% of authors of guideline-related publications.
CONCLUSIONS: The important imbalance between the geographical distribution of lived experience with MDR/RR-TB and the distribution of individuals generating knowledge and guidance on treatment of MDR/RR-TB can have clinical and resource

implications. Countries may reject or defer guideline adoption because of a mismatch between that guidance and local disease epidemiology. Funding conditioned on compliance with guidelines can exacerbate health inequalities. The movement to decolonize global health considers representation disparities as epistemic injustice, that is unfair treatment in the process of generating, sharing, or receiving knowledge. Reform is possible in many of the institutions involved in generation of global health knowledge, such as: meaningful participation of LLMICs in projects as a requirement for research funding, improved attention to the epistemic and geographical location of journal editorial staff, and broader inclusion in guidelines committees. Better alignment of participation in knowledge generation with burden of disease holds potential for reducing inequality and improving relevance of guidance for the lived experience with MDR/RR-TB.

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15. Drug-resistant tuberculosis in Malaysia: Prevalence, characteristics, and treatment outcomes.

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INTRODUCTION: Drug-resistant tuberculosis (DR-TB) poses a serious global health threat, leading to high morbidity and mortality rates. Malaysia has witnessed an increase in DRTB cases, necessitating research into trends and characteristics. This study aims to determine the prevalence and describe the characteristics and treatment outcomes of DR-TB cases in Malaysia from 2016 to 2020.
MATERIALS AND METHODS: A retrospective record review was carried out, utilising secondary data obtained from the TB registry of Selangor and Wilayah Persekutuan Kuala Lumpur. All registered DR-TB cases between 2016 and 2020 that met the

study criteria were analysed descriptively using SPSS software version 27.
RESULTS: Of 443 cases of registered DR-TB over 5 years, 430 cases fulfilled the study criteria. The prevalence of DR-TB increased from 0.27 to 1.79 per 100,000 population between 2016 and 2020. The average age was 40.96 years, majority were males (70.7%), Malaysian (79.3%), with Malays comprising 50.2%. Most patients had up to secondary school education (51.9%), married (57.0%), employed (53.3%) and 34.9% were smokers. For clinical characteristics, 23.5% had diabetes, and 10.9% were HIVpositive. Retreatment cases accounted for half the total, and 83.9% had positive smear results. Minimal chest X-ray lesions were observed in 54.4% of cases. The majority (66.7%) received supervised treatment from healthcare providers after being diagnosed with DR-TB, and 37.4% had more than one anti-TB resistance. Favourable treatment outcomes were observed in 56.7% of cases, while 42.1% had unfavourable outcomes, mainly due to loss to follow-up (49.7%), death (42.6%) and treatment failure (7.7%).
CONCLUSION: The rising cases of DR-TB call for comprehensive public health interventions and stakeholder commitment to reduce its occurrence and transmission. These findings provide valuable guidance for policymakers in strengthening DR-TB control and prevention strategies.

PMID: 39614782 [Indexed for MEDLINE]

16. The health-related quality of life of drug-resistant tuberculosis patients receiving treatment in Botswana.

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BACKGROUND: Drug-resistant tuberculosis (DR-TB) poses a significant global health challenge and requires treatment with potentially toxic second-line anti-TB drugs. Assessing the health-related quality of life (HRQoL) of DR-TB patients is crucial, given the impact of disease and treatment on their well-being. This study aimed to evaluate HRQoL among DR-TB patients undergoing treatment in Botswana and identify predictors of variability during the treatment period.
METHODS: A cross-sectional study involving almost all the eligible clients in the DR-TB treatment database was conducted at four of the six DR-TB sites in

Botswana. The SF-36v2-based questionnaire was administered to all patients receiving treatment between March 2022 and June 2023. Data analysis was performed with QualityMetric Inc., LLC PRO CoRE scoring software and Stata 13.1 for the HRQoL scoring and regression analyses, respectively. A score ≤ 47 on the norm-based scoring (NBS) indicated poor HRQoL. Shorter, all-oral DR-TB regimens were introduced since 2018 but Botswana had not yet fully implemented those in the years 2022/2023. Patients had to go on treatment for 18-24 months during the time of the study.
RESULTS: Seventy-two of the 81 eligible participants were enrolled. Participants on treatment for 13-24 months exhibited better HRQoL scores (53.3 ± 8.4) than those in the initial (0-12 months, 46.9 ± 10.8) and latter phases of treatment (> 24 months, 44.3 ± 10.1) for the Physical Component Summary (PCS) even though it was not statistically significant (p = 0.0996). The mental component summary (MCS) scores were 41.6 ± 11.3, 51.6 ± 7.8, and 41.3 ± 10.7 for 0-12, 13-24, and > 24 months, respectively, with significant differences observed for the MCS (p = 0.0097). Multivariate analysis identified renal impairment as a predictor of PCS variability, while alcohol consumption, prior TB treatment, and lung cavity on chest X-ray imaging predicted MCS variability.
CONCLUSION: DR-TB patients in Botswana demonstrated comparable or improved HRQoL (> 47 NBS) in their second year (13-24 months) of treatment, contrasting with poorer HRQoL scores in the initial and final years for both the PCS and MCS. The findings underscore the necessity for tailored psychosocial support, advocated for its integration into the Botswana National TB Program as a pilot initiative before widespread implementation.

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PMID: 39614181 [Indexed for MEDLINE]

Conflict of interest statement: Declarations. Ethical approval and consent to participate: All ethical clearance procedures were followed before the start of the study. Ethical approval was obtained from the University of Botswana Institutional Review Board (IRB) under reference number UBR/RES/IRB/BIO/GRAD/158 and the Ministry of Health Review Board under permit number HPDME: 13/18/1 of 01 December 2021, and permission to conduct the study on sites was granted by the PMH, NRH, SMH and GPH IRBs. All respondents were requested to sign a consent form and were informed that participation in the study is voluntary. All participants who successfully completed the study questionnaire were included in the analysis. All participants provided written informed consent before study participation. Clinical trial number: not applicable. Consent for publication: Not applicable. Competing interests: The authors declare no competing interests.

17. Triage test for all-oral drug-resistant tuberculosis (DR-TB) regimen: a phase IV study to assess effectiveness, feasibility, acceptability and cost-effectiveness

of the Xpert MTB/XDR assay for rapid triage and treatment of DR-TB.

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INTRODUCTION: The TriAD study will assess the Xpert MTB/XDR (Xpert XDR; Cepheid) assay to detect tuberculosis (TB) drug resistance in sputum testing positive for TB to rapidly triage and treat patients with a short all-oral treatment regimen.
METHODS AND ANALYSIS: In this study, approximately 4800 Xpert MTB/RIF or Ultra MTB-positive patients (irrespective of rifampicin (RIF) resistance (RR) status) from several clinical sites across South Africa, Nigeria and Ethiopia will be enrolled over 18-24 months and followed-up for approximately 6 months post-TB

treatment completion. Participants will be enrolled into one of two cohorts based on Xpert MTB/RIF and Xpert XDR results: Mycobacterium tuberculosis (M.tb) positive participants with RR in Cohort 1 (n=880) and M.tb positive RIF susceptible TB patients with isoniazid mono-resistance irrespective of presence of resistance to fluoroquinolones, second-line injectable drugs or ethionamide in Cohort 2 (n=400). Cohort 1 will be compared with historical cohorts from each implementing sites. The primary study outcomes include time to initiation of an appropriate treatment regimen by resistance profile and the proportion of patients with favourable treatment outcomes compared with historical cohorts from each of the implementing sites. Secondary outcomes include feasibility, acceptability and cost-effectiveness of this approach to inform policies and guidelines for programmatic implementation of this triage and treat model for drug-resistant tuberculosis management. Utility of the tuberculosis molecular bacterial load assay (TB-MBLA) for real-time treatment response assessment will also be evaluated.
ETHICS AND DISSEMINATION: The University of KwaZulu-Natal Biomedical Research Ethics Committee (BREC) and local research committees have provided ethical review and approval (BREC/00002654/2021, HREC 210805, NHREC/01/01/2007 and EPHI-IRB-459-2022). The South African Health Products Regulatory Authority (SAHPRA) have granted regulatory approval for the TRiAD Study (SAHPRA MD20211001). Trial results will be disseminated through conference presentations, peer-reviewed publications and the clinical trial registry.
TRIAL REGISTRATION NUMBER: Clinicaltrials.gov; Trial registration number: NCT05175794; South African National Clinical Trials Register (SANCTR DOH-27-012022-4720).

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18. Analysis of the Results of Tuberculosis Drug Resistance Surveillance in Yuexiu District, Guangzhou City, 2013-2022.

Immun Inflamm Dis. 2024 Nov;12(11):e70060. doi: 10.1002/iid3.70060.

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INTRODUCTION: The objectives of the study are to understand the drug-resistant situation and trend of tuberculosis patients in Yuexiu District, Guangzhou City, from 2013 to 2022, and to provide a scientific basis for the development of rational drug-resistant tuberculosis prevention and control strategies in Guangzhou City.
METHODS: All patients who were diagnosed with active tuberculosis in Guangzhou Chest Hospital from January 1, 2013 to December 31, 2022 were collected as study subjects, and a total of 5191 patients were enrolled in the study. Comprehensive data on the basic characteristics, diagnostic, and therapeutic information of the study subjects were collected. Sputum specimens were subjected to smear, isolation, and culture. Culture-positive strains of bacteria were identified by bacterial groups. A total of 1659 strains of Mycobacterium tuberculosis (MTB) isolates were obtained. The drug susceptibility test was carried out using the proportionality method on the MTB isolates for nine types of antituberculosis medicines: isoniazid (INH), rifampicin (RFP), ethambutol (EMB), streptomycin (Sm), kanamycin (Km), ofloxacin (Ofx), capreomycin (Cm), propylthioisonicotinamide (Pto), and p-aminosalicylic acid (PAS). A comparative analysis of the resistance patterns among the strains was conducted.
RESULTS: A total of 1659 patients with MTB were cultured, revealing 438 drug-resistant cases. Among these, 255 were monoresistant, 121 were polyresistant, and 62 were multidrug resistant. The overall resistance rate was 26.40% (438/1659), with mono-resistance rate at 15.37% (255/1659), polyresistance rate at 7.29% (121/1659), and multidrug resistance rate at 3.74% (62/1659). In descending order, the resistance rates of MTB isolates to any of the nine antituberculosis drugs were Sm (12.24%, 203/1659), INH (9.22%, 153/1659), EMB (7.35%, 122/1659), RFP (6.99%, 116/1659), PAS (3.25%, 54/1659), Pto (3.13%, 52/1659), Ofx (2.71%, 45/1659), Cm (2.17%, 36/1659), and Km (2.17%, 36/1659). The differences in resistance rates were statistically significant ($p < 0.01$), with Sm exhibiting the highest resistance rate and Km the lowest. In the primary treatment group, 388 patients (25.55%) were drug resistant, while 50 patients (35.46%) in the retreatment group were drug resistant. Thirty-nine patients (2.57%) in the primary treatment group were multidrug resistant, compared to 23 patients (16.31%) in the retreatment group. The resistance rate and multidrug resistance rate of isolates from retreatment patients were significantly higher than primary treatment patients ($p < 0.05$).
CONCLUSIONS: The problem of drug-resistant tuberculosis transmission in Guangzhou requires attention, and drug-resistant screening should be further increased to effectively control the source of infection.

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

19. Small Molecule Inhibitors of Mycobacterium tuberculosis Topoisomerase I Identified by Machine Learning and In Vitro Assays.

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Tuberculosis (TB) caused by Mycobacterium tuberculosis is a leading infectious cause of death globally. The treatment of patients becomes much more difficult for the increasingly common multi-drug resistant TB. Topoisomerase I is essential for the viability of M. tuberculosis and has been validated as a new target for the discovery of novel treatment against TB resistant to the currently available drugs. Virtual high-throughput screening based on machine learning was used in this study to identify small molecules that target the binding site of divalent ion near the catalytic tyrosine of M. tuberculosis topoisomerase I. From the virtual screening of more than 2 million commercially available compounds, 96 compounds were selected for testing in topoisomerase I relaxation activity assay. The top hit that has IC50 of 7 μM was further investigated. Commercially available analogs of the top hit were purchased and tested with the in vitro enzyme assay to gain further insights into the molecular scaffold required for topoisomerase inhibition. Results from this project demonstrated that novel small molecule inhibitors of bacterial topoisomerase I can be identified starting with the machine-learning-based virtual screening approach.

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current employee and holds equity in Atomwise, Inc.

20. Identifying Predictors of Unfavorable Treatment Outcomes in Tuberculosis Patients.

Int J Environ Res Public Health. 2024 Oct 31;21(11):1454. doi: 10.3390/ijerph21111454.

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OBJECTIVES: In South Korea, there has been a continuous decrease in the incidence of tuberculosis (TB) attributable to a national TB elimination program; however, TB still poses a significant socioeconomic burden. This study aimed to analyze factors associated with successful TB treatment and to identify refractory patient groups with unfavorable outcomes.
METHODS: We analyzed anonymized data on 89,150 patients with TB provided by the Korea Disease Control and Prevention Agency. Specifically, we collected independent variables, which were categorized as individual, regional, and medical facility factors. Individual factors included age, sex, nationality, TB type, drug-resistant status, category of TB, housing type, underlying disease status, number of referrals, and smoking status. Regional factors referred to the region where the TB case was reported. Medical facility factors included the first visit to a medical facility, categorized by hospital type and the distinction between private-public mix (PPM) and non-PPM depending on the presence or absence of dedicated TB nurses. These factors were analyzed in relation to treatment success to identify refractory patient groups with unfavorable outcomes.
RESULTS: Multivariable logistic regression analysis revealed the following significant factors associated with successful TB treatment: sex, nationality, status of drug-resistant TB, category of TB, number of referrals, region of TB registry, underlying diseases, and smoking status. Specifically, compared with their relevant counterparts, male patients had a lower rate of successful treatment (adjusted odds ratio [aOR]: 0.66, reference [Ref.]: women); Korean nationals had a higher rate of treatment success (aOR: 7.20, Ref. foreign residents in Korea); resistant TB was associated with a lower rate of treatment success (aOR: 0.35, Ref.: non-resistant TB status); newly treated patients had a

higher rate of treatment success (aOR: 1.75, Ref.: retreatment patient); switching hospitals once (aOR: 1.78), never (aOR: 1.41), or twice (aOR: 1.37) was associated with increased treatment success (Ref.: three or more times); having zero (aOR: 1.45), one (aOR: 1.31), or two (aOR: 1.24) underlying diseases was associated with a higher rate of treatment success (Ref. three or more underlying diseases); and past smokers (aOR: 1.40) and non-smokers (aOR: 1.35) had a higher rate of treatment success (Ref.: current smokers).
CONCLUSIONS: Our study identified several factors contributing to unfavorable treatment outcomes in tuberculosis patients, including male patients, foreign residents in Korea, drug-resistant TB, retreatment patients, frequent hospital switching, multiple underlying diseases, and current smoking status. These research findings could inform the development of efficient management strategies and policies for improving the treatment success rate among patients with TB.

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21. Assessing the Impact of Bedaquiline, Clofazimine, and Linezolid on Mycobacterial Genome Integrity.

Biomolecules. 2024 Nov 15;14(11):1451. doi: 10.3390/biom14111451.

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Tuberculosis (TB) presents significant medical challenges, largely due to the genetic diversity of Mycobacterium tuberculosis, which enhances the resilience and resistance of the pathogen to first-line treatments. In response to the global rise of drug-resistant TB, second-line antitubercular drugs like bedaquiline (BDQ), linezolid (LZD), and clofazimine (CFZ) have become critical treatment options. Understanding the molecular changes these drugs induce is essential for optimizing TB therapy. To contribute to this effort, we investigated their impact on genome maintenance and stability using Mycobacterium smegmatis as a model organism. Using mutation accumulation assays and whole-genome sequencing, we found that the second-line antibiotics did not significantly increase mutation rates, unlike the positive control UV treatment. However, upon BDQ treatment, we detected mutations in transporter proteins and

transcription factors without any increase in the minimal inhibitory concentration. Additionally, BDQ and CFZ were found to alter DNA repair pathways and reduce cellular dNTP levels, particularly CFZ, which depleted dGTP, impacting DNA synthesis. CFZ also upregulated DNA repair enzymes, enhancing error-free repairs. Despite minimal mutagenic effects, both drugs displayed distinct impacts on cellular mechanisms, suggesting additional modes of action.

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22. Mycobacterium tuberculosis: The Mechanism of Pathogenicity, Immune Responses, and Diagnostic Challenges.

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BACKGROUND: The infection caused by Mycobacterium tuberculosis arises from a complex interplay between the host immune system and the bacteria. Early and effective treatment of this disease is of great importance in order to prevent the emergence of drug-resistant strains. This necessitates the availability of fast and reliable diagnostic methods for managing affected cases. One reason why

this study is significant is the lack of a comprehensive review in this field that thoroughly examines the importance, pathogenesis, and diagnosis of M. tuberculosis. Therefore, the aim of this review is to provide updated information on M. tuberculosis.
METHODS: We investigate the virulence factors, pathogenicity, and diagnostic methods of this bacterium, alongside the clinical symptoms and interpretation of different types of tuberculosis, including cerebral, miliary, nerve, and tubercular tuberculosis.
RESULTS: Mycobacterium tuberculosis acts as the causative agent of human tuberculosis and is regarded as one of the most adaptable human pathogens. M. tuberculosis possesses several virulence factors that help the bacterium evade mucous barriers. The rise of multidrug-resistant tuberculosis (MDR-TB) in both developing and industrialized countries emphasizes the need for rapid diagnostic methods.
CONCLUSIONS: Non-protein virulence factors play a crucial role in the pathogenicity of Mycobacterium tuberculosis (M. tuberculosis). The bacterial cell membrane contains proteins that modulate the host immune response. For instance, ESAT-6, either alone or in combination with CFP-10, reduces immune activity. While molecular techniques-such as DNA microarray, luciferase reporter assay, polymerase chain reaction (PCR), DNA and RNA probes, next-generation sequencing, and whole-genome sequencing-offer rapid, sensitive, and specific detection of M. tuberculosis, these methods are expensive and require technical expertise.

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PMID: 39593272 [Indexed for MEDLINE]

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

23. A Multi Center, Epidemiological Study of Bone Tuberculosis in Southwest China from 2011 to 2023.

J Epidemiol Glob Health. 2024 Dec;14(4):1678-1692. doi: 10.1007/s44197-024-00325-2. Epub 2024 Nov 18.

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BACKGROUND: Despite continued efforts to manage and control Tuberculosis (TB) in China, it remains a major health concern. Bone tuberculosis (Bone-TB), a common form of extrapulmonary tuberculosis, still adds considerably to the global TB case load. Diagnosing Bone-TB is often difficult as its symptoms can be similar to other bone or joint diseases, which leads to delayed detection and treatment. Currently, comprehensive reports on the epidemiological aspects of Bone-TB in China are scarce.
METHODS: This retrospective study analyzed demographic and clinical data from 2,191 patients diagnosed with Bone-TB in Southwest China between January 2011 and September 2023.This study fully reveals the characteristics of Bone-TB in Southwest China.
RESULTS: The overall trend of bone tuberculosis was a slow rise. Among 2191 patients, males, farmers, aged 42-68 years, and people with HIV and diabetes are the priority groups for the prevention and treatment of Bone-TB. The majority of the infected spines (1556/2191) were located in the thoracic vertebra (759/2191) and lumbar vertebra (715/2191). Forty-nine (2.24%) patients had drug-resistant TB (DR-TB). Forty-five (2.05%) died during the treatment. The total and actual hospitalization. Costs amounted to $3,837.10 and $1,914.35 ($p < 0.01$). Patients with DR-TB incurred the highest costs, amounting to $4,968.37. Cervical TB, with a prevalence of 5 patients (6.10%), exhibited the highest rates of catastrophic expenditures.
CONCLUSIONS: From 2011 to 2023, the yearly occurrence of Bone-TB in southwestern China exhibited a rising pattern, marked by notable distinctions in terms of gender, age, and regional variations, indicating localized clustering characteristics.

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PMID: 39556304 [Indexed for MEDLINE]

Conflict of interest statement: Declarations. Ethics Approval and Consent to Participate: As per the Ethics Committee of the First Affiliated Hospital of Guangxi Medical University and the Fourth People’s Hospital of Nanning, written informed consent from each patient was deemed unnecessary for this study due to the removal of all sensitive patient information prior to analysis. The study

adhered to the principles of the Declaration of Helsinki and received approval from the Ethics Committee of the Fourth People's Hospital of Nanning and the First Affiliated Hospital of Guangxi Medical University (Approval number: 2023-36-01, NO.2022-KY-E-152). Consent for Publication: Not applicable. Competing Interests: The authors declare no competing interests.

24. Modeling the epidemiologic impact of age-targeted vaccination for drug-resistant tuberculosis.

Drug Resist Updat. 2025 Jan;78:101172. doi: 10.1016/j.drup.2024.101172. Epub 2024 Nov 13.

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This study used a calibrated mathematical model to evaluate age-specific tuberculosis (TB) vaccination strategies, for drug-resistant (DR)-TB management in China. Prioritizing elderly vaccination significantly reduced multidrug-resistant or rifampicin-resistant TB incidence and mortality, while avoiding the need for second-line treatment, offering a promising approach to mitigate DR-TB burden by 2050.

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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.

25. Treatment of Mycobacterium tuberculosis infected macrophages with Rifabutin loaded β-glucan microparticles induces macroautophagy mediated bacillary killing.

Int J Biol Macromol. 2024 Dec;283(Pt 2):137256. doi: 10.1016/j.ijbiomac.2024.137256. Epub 2024 Nov 9.

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Tuberculosis (TB), attributable to Mycobacterium tuberculosis (M.tb.), constitutes a formidable global health challenge, particularly with the proliferation of multidrug-resistant (MDR-TB) strains. The efficacious clearance

of M.tb. from host cells is imperative for mitigating infection and averting disease progression. Autophagy, an intricate cellular mechanism for degrading and recycling biomolecules, plays a pivotal role in the immune response to M.tb. by facilitating the degradation of intracellular pathogen through the formation of autophagosomes and their subsequent fusion with lysosomes. The present study elucidates the therapeutic efficacy of Rifabutin loaded YDGP (DYDGP) microparticles within M.tb.infected macrophage. Our results show that the administration of DYDGP improve the membrane integrity of macrophage infected with H37Rv as well as MDR strains, as compared to that of untreated controls at 30 min, 6 h and 24 h post-exposure time points. DCFHDA staining elucidated that DYDGP treatment significantly enhances intracellular reactive oxygen species (ROS) production compared to blank YDGP, even in the presence of NOX-2 inhibitors. Furthermore, DYDGP promotes the biogenesis of acidic vesicular organelles and phago-lysosomal maturation, as corroborated by acridine orange and Lysotracker Red staining. Immunofluorescence and dansylcadaverine dual staining data evidenced that DYDGP treatment enhances autophagosome formation, autophagy induction and LC3 puncta formation within M.tb. infected macrophage at both 30 min and 24 h post-exposure time points. Further, protein expression analyses demonstrated that DYDGP treatment enhances the expression levels of NOX-2 and LC3, thereby confirming autophagy induction within M.tb. infected macrophage. Antimycobacterial efficacy assessments revealed that DYDGP treatment engendered significant reductions in colony-forming units (CFUs) of H37Rv (64, 40, 19), MDR32420 (44, 35, 18), MDR32422 (44, 39, 21), and MDR32521 (38, 22, 18) after 30 min, 24 h, and 48 h, exposure respectively. These findings accentuate DYDGP's potential to substantially attenuate M.tb. burden, including the addressal of MDR strains, thereby positioning it as a promising adjunctive therapy for augmenting TB treatment.

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

26. Cryo-EM structure of the Mycobacterium smegmatis MmpL5-AcpM complex.

mBio. 2024 Dec 11;15(12):e0303524. doi: 10.1128/mbio.03035-24. Epub 2024 Oct 31.

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Mycobacterium tuberculosis, the causative agent of the airborne infection tuberculosis (TB), contains 13 mycobacterial membrane protein large (MmpL) transporters that can be divided into two distinct subclasses. These MmpL proteins play important functional roles within the mycobacterium and subsequently are considered attractive drug targets to combat TB infection. Previously, we reported both X-ray and cryo-electron microscopy (cryo-EM) structures of the MmpL3 transporter, providing high-resolution structural information for this subclass of the MmpL proteins. Thus far, there is no structural information available for the other subclass, which includes MmpL5, an inner membrane transporter that plays a critical role in iron hemostasis. Here, we report the first cryo-EM structure of the Mycobacterium smegmatis MmpL5 transporter bound with the meromycolate extension acyl carrier protein M (AcpM) to a resolution of 2.81 Å. Our structural data reveals that MmpL5 and AcpM interact in the cytoplasm to form a complex, and this allows us to propose that MmpL5 may also associate with the mycobactin L (MbtL) protein in a similar fashion to form a heterocomplex important for iron acquisition, which enables the survival and replication of the mycobacterium.
IMPORTANCE: The emergence and spread of multidrug-resistant tuberculosis (TB) present enormous challenges to the global public health. The causative agent, Mycobacterium tuberculosis, has now infected more than one-third of the world's population. Here, we report the first structure of the mycobacterial membrane protein large 5 (MmpL5), an essential transporter for iron acquisition, bound with the meromycolate extension acyl carrier protein M (AcpM), indicating a plausible pathway for mycobactin translocation. Our studies will ultimately inform an era in structure-guided drug design to combat TB infection.

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27. Frameshift mutations in the mmpR5 gene can have a bedaquiline-susceptible phenotype by retaining a protein structure and function similar to wild-type Mycobacterium tuberculosis.

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Bedaquiline (BDQ) is crucial for the treatment of rifampicin-resistant tuberculosis, yet resistance threatens its effectiveness, mainly linked to mutations in the mmpR5 (Rv0678) gene. While frameshift mutations are thought to produce non-functional proteins, we hypothesize that they can result in conserved proteins through late-stop codons or alternative reading frames and remain BDQ susceptible. We extracted 512 isolates harboring frameshift mutations in mmpR5 from the World Health Organization (WHO) catalog and 68 isolates with minimum inhibitory concentration (MIC) in mycobacterial growth indicator tube (MGIT) through a literature review. Using BioPython and AlphaFold2 we computed open (ORF) and alternative reading frames (ARFs) sequences and protein structures and assessed similarity to the wild type using an alignment and template modeling (TM)-score. Among the WHO 512 isolates, 24.8% were BDQ-sensitive. Out of 184 unique frameshift mutations with available nucleotide information, a late-stop codon in the ORF occurred for 32% of the mutations. Also, 40.7% resulted in a conserved sequence, through the ORF or one of the forward ARFs. In 68 isolates with available MGIT MIC data, the presence of late-stop codons in the ORF (OR 4.71, 95% CI 1.36-19.3) or a conserved reading frame (OR 10.4, 95% CI 2.07-102.9) were associated with BDQ sensitivity. Protein structures from the conserved sequences showed high similarity (TM > 0.8). We show that frameshift mutations may retain BDQ susceptibility through late-stop codons in the ORF or conserved ARFs. These findings could improve the prediction of the BDQ phenotype from genomic data and have important implications for treatment decisions. Research Foundation-Flanders, Academy of Medical Sciences, the Wellcome Trust, the Government Department of Business, Energy and Industrial Strategy, the British Heart Foundation and Diabetes UK, and the Global Challenges Research Fund.IMPORTANCETuberculosis (TB), caused by Mycobacterium tuberculosis, remains the deadliest infectious disease and is particularly challenging to treat when it becomes drug-resistant. Bedaquiline (BDQ) is a recently recommended core drug for treating drug-resistant TB. However, resistance to bedaquiline is already emerging, primarily due to mutations in the mmpR5 gene. Identifying which mutations cause resistance and which do not is a critical knowledge gap. In particular, little is known about the effect of frameshift mutations, typically thought to make TB bacteria resistant to bedaquiline by producing non-functional proteins. Yet, one-quarter of isolates with a frameshift mutation are still susceptible to bedaquiline. How the bacteria produce a functional protein despite the frameshift mutation is

unknown. We analyzed over 500 frameshift mutations using computational methods to model their effects on protein structure and bedaquiline resistance. Our findings revealed that some frameshift mutations can still produce functional proteins, allowing bacteria to remain sensitive to bedaquiline. Specifically, bacteria can produce a functional protein despite frameshift mutations if the mutation occurs near the end of the protein or if an alternative reading frame is available. These insights improve our ability to interpret mutations associated with bedaquiline, the most important drug for drug-resistant TB, allowing more accurate and effective treatment decisions.

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

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

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PMID: 39426632 [Indexed for MEDLINE]

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

29. Linezolid Pharmacokinetic-Anemia Modeling in Children With Rifampicin-Resistant Tuberculosis.

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

CONCLUSIONS: Taken together, these data confirm currently recommended linezolid doses for children. The risk of anemia in children should be carefully considered and monitored. Initiating linezolid in children with low baseline hemoglobin increases the probability of experiencing grade 3 or 4 anemia.

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

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BACKGROUND: Tuberculosis (TB) is a preventable and treatable disease leading to the second death globally. The evolution of drug resistance in Mycobacterium tuberculosis (MTB), particularly rifampicin resistance (RR), has hampered TB control efforts. Thus, this study aimed to provide information regarding the magnitude of MTB and rifampicin resistance among patients tested using the GeneXpert method.
METHODS: A retrospective analysis was carried out at DTCSH. The study included TB registration logbook data from all patients who visited the hospital and were tested for MTB with the Xpert MTB/RIF assay from 2017 to 2024. The laboratory-based data were entered, cleaned, and analyzed using SPSS version 26 software. Multilogistic regression analysis was employed, and a p value ≤ 0.05 was considered statistically significant.

RESULTS: A total of 12,981 patient results were included, of which 8.9% (1160/12,981) were MTB-positive and 7.1% (82/1160) were RR. Individuals aged 15-29 years (AOR = 2.13; 95% CI = 1.55-2.93, p < 0.001), living in rural areas (AOR = 1.23; 95% CI = 1.08-1.41, p = 0.003), and HIV+ (AOR = 1.79; 95% CI = 1.48-2.33, p < 0.001) had a higher risk of developing tuberculosis. While RR was identified in 63.4% (52/82) of new, 24.4% (20/82) of re-treated, and 12.2% (10/82) of failed presumptive TB patients.
CONCLUSION: In this study, MTB and RR trends were high. Productive age groups, rural populations, and HIV patients were at risk. To lessen the burden of this contagious and fatal disease, it is recommended to increase early diagnosis of drug-resistant TB and enhance infection control.

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31. Long-term efficacy and safety of two short standardised regimens for the treatment of rifampicin-resistant tuberculosis (STREAM stage 2): extended follow-up of an open-label, multicentre, randomised, non-inferiority trial.

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BACKGROUND: STREAM stage 2 showed that two bedaquiline-containing regimens (a 9-month all-oral regimen and a 6-month regimen with 8 weeks of aminoglycoside) had superior efficacy to a 9-month injectable-containing regimen for rifampicin-resistant tuberculosis up to 76 weeks after randomisation. Our objective in this follow-up analysis was to assess the durability of efficacy and safety, including mortality, at 132 weeks.
METHODS: We report the long-term outcomes from STREAM stage 2, a randomised, phase 3 non-inferiority (10% margin) trial in participants (aged ≥15 years) with rifampicin-resistant tuberculosis without fluoroquinolone or aminoglycoside resistance at 13 clinical sites in seven countries (Ethiopia, Georgia, India, Moldova, Mongolia, South Africa, and Uganda). Participants were randomly assigned 1:2:2:2 (via permuted blocks and stratified by site and HIV status plus CD4 cell count) to the 2011 WHO long regimen (terminated early), a 9-month control regimen, a 9-month oral regimen with bedaquiline (primary comparison), or a 6-month regimen with bedaquiline and 8 weeks of an injectable antituberculous drug. Participants and clinicians were aware of treatment-group assignments, but laboratory staff were masked. The primary outcome, reported previously, was favourable status (negative cultures for Mycobacterium tuberculosis without a preceding unfavourable outcome; any death, bacteriological failure or recurrence, and major treatment change were considered unfavourable) at week 76. Here we report efficacy outcomes at week 132, analysed in the modified intention-to-treat (mITT) population. Safety

assessments continued to 132 weeks and were in all participants who received at least one dose of the study regimen. All comparisons used concurrently randomised participants. This trial is registered on ISRCTN (ISRCTN18148631) and is now completed.
FINDINGS: Between March 28, 2016, and Jan 28, 2020, 588 participants were randomly assigned to the long (n=32), control (n=202), oral (n=211), or 6-month (n=143) treatment regimens; 352 (60%) were male and 236 (40%) were female. Of the 556 participants on the three shorter regimens, 517 were included in the mITT population (187 in control group, 196 in oral group, and 134 in 6-month group) and 465 in the per-protocol analyses. Six additional participants had an unfavourable outcome that occurred between week 76 and the end of efficacy follow-up (one in control group, four in oral group, one in 6-month group). In the mITT population, the proportion of patients with an unfavourable outcome at the end of follow-up was 19·6% (95% CI 14·3 to 24·9) in the oral group and 29·3% (23·3 to 36·5) in the control group (-9·7 percentage points difference [95% CI -18·7 to -1·8]; psuperiority=0·024). An estimated 9·8% (95% CI 4·6 to 14·9) of participants on the 6-month regimen had an unfavourable outcome, which was significantly lower than for those concurrently on the control regimen (32·5% [23·7 to 40·2]; psuperiority<0·0001) or the oral regimen (23·8% [16·9 to 31·1]; psuperiority=0·013). Few serious or severe adverse events were reported after week 76, with no indication of a difference between the regimens. At week 132, treatment-emergent hearing loss was recorded in significantly fewer participants on the oral regimen (7/205; 3%) than the control regimen (16/198; 8%; p=0.041); there was no significant difference in severe hearing loss between the oral regimen (6/139; 4%) and the 6-month regimen (5/143; 4%; p=0·72). Death rates were low: 1·01 (95% CI 0·48 to 2·12) per 100 person-years in participants allocated to bedaquiline (ie, oral and 6-month regimen, n=287) compared with 1·52 (0·63 to 3·66) in participants on the control regimen (n=140; p=0·49).
INTERPRETATION: Both of the bedaquiline-containing regimens maintained superiority to the control regimen, without evidence of increased mortality, providing two additional evidence-based treatment options for patients; previous mortality concerns for bedaquiline were not substantiated.
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32. Evaluating the efficacy of whole genome sequencing in predicting susceptibility profiles for first-line antituberculosis drugs.

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OBJECTIVES: This study aimed to examine the efficacy of whole genome sequencing (WGS) in accurately predicting susceptibility profiles, potentially eliminating the need for conventional phenotypic drug susceptibility testing (pDST) for first-line antituberculosis drugs in routine tuberculosis diagnosis.
METHODS: Over the period of 2017 to 2020, 1114 Mycobacterium tuberculosis complex isolates were collected with drug susceptibility testing conducted using the MGIT960 system and WGS performed for predicting drug resistance profiles. In addition, we implemented a new algorithm with an updated WGS workflow, omitting pan-susceptible strains from pDST.
RESULTS: Results showed that out of 1075 analysed isolates, WGS-based genotypic sensitivity predictions for isoniazid, rifampicin, ethambutol, and pyrazinamide were 100% (95% CI, 99.6-100%), 100% (95% CI, 99.62-100%), 99.8% (95% CI, 99.26-99.94%), and 100% (95% CI, 99.63-100%), respectively. In contrast, the WGS-based genotypic resistance prediction, was 98.85% (95% CI, 93.77-99.79%) for isoniazid, 94.74% (95% CI, 82.71-98.54%) for rifampicin, 86.96% (95% CI, 67.87-95.46%) for ethambutol, and 75.7% (95% CI, 59.9-86.63%) for pyrazinamide. Moreover, WGS enabled the implementation of a new testing algorithm that made it

unnecessary to perform pDST in 954 of all 1075 samples (88.7%) and in 890 of 901 pan-susceptible samples (98.8%).
DISCUSSION: Integrating WGS into tuberculosis management offers significant potential to replace phenotypic drug susceptibility testing, especially for problematic drugs like pyrazinamide and ethambutol, potentially improving treatment outcomes.

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

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Mycobacteria are opportunistic intracellular pathogens that have plagued humans and other animals throughout history and still are today. They manipulate and hijack phagocytic cells of immune systems, enabling them to occupy this peculiar infection niche. Mycobacteria exploit a plethora of mechanisms to resist antimicrobials (e. g., waxy cell walls, efflux pumps, target modification, biofilms, etc.) thereby evolving into superbugs, such as extensively drug-resistant tuberculosis (XDR TB) bacilli and the emerging pathogenic Mycobacterium abscessus complex. This review summarizes the mechanisms of action of some of the surging antimycobacterial strategies. Exploiting the fact that mycobacteria are obligate aerobes and the differences between their oxidative phosphorylation pathways versus their human counterpart opens a promising avenue for drug discovery. The polymorphism of respiratory complexes across mycobacterial pathogens imposes challenges on the repositioning of antimycobacterial agents to battle the rise in nontuberculous mycobacterial infections. In silico strategies exploiting mycobacterial respiratory machinery data to design novel therapeutic agents are touched upon. The potential druggability of mycobacterial respiratory elements is reviewed. Future research addressing the health challenges associated with mycobacterial pathogens is

discussed.

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34. Bedaquiline: what might the future hold?

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Tuberculosis drug development has stagnated for decades, so the recent availability of bedaquiline is welcome. Bedaquiline-containing regimens, now the first-line therapy recommended by WHO, have transformed the treatment of drug-resistant tuberculosis, offering safer and more effective oral treatment options. However, key obstacles need to be overcome to ensure global access and prevent the rapid development of resistance against this promising class of drugs. In this Personal View, building on an international workshop held in 2023, we evaluate the current evidence and suggest possible ways forward, recognising the tension between increasing use and slowing the rise of resistance. We also discuss problems in accessing bedaquiline-containing regimens, the potential widening of their use beyond drug-resistant tuberculosis, and lessons for utilising new drugs as they are developed.

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Partnership, and owns TB Drug Monographs. LL has received funding from Gilead Sciences Inc and support for travel from Roche.

35. Accurate and affordable detection of rifampicin and isoniazid resistance in Tuberculosis sputum specimens by multiplex PCR-multiple probes melting analysis.

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BACKGROUND: Escalating cases of multidrug-resistant tuberculosis (MDR-TB) pose a major challenge to global TB control efforts, necessitating innovative diagnostics to empower decentralized detection of gene mutations associated with resistance to rifampicin (RIF) and isoniazid (INH) in Mycobacterium tuberculosis (M. tuberculosis) in resource-constrained settings.
METHODS: Combining multiplex fluorescent PCR and Multiple Probes Melting Analysis, we identified mutations in the rpoB, katG, ahpC and inhA genes from sputum specimens. We first constructed a reference plasmid library comprising 40 prevalent mutations in the target genes' resistance determining regions and promoters, serving as positive controls. Our assay utilizes a four-tube asymmetric PCR method with specifically designed molecular beacon probes, enabling simultaneous detection of all 40 mutations. We evaluated the assay's

effectiveness using DNA isolated from 50 clinically confirmed M. tuberculosis sputum specimens, comparing our results with those obtained from Sanger sequencing and retrospective validation involving bacteriological culture and phenotypic drug susceptibility testing (pDST). We also included the commercial Xpert MTB/RIF assay for accuracy comparison.
RESULTS: Our data demonstrated remarkable sensitivity in detecting resistance to RIF and INH, achieving values of 93.33% and 95.24%, respectively, with a specificity of 100%. The concordance between our assay and pDST was 98.00%. Furthermore, the accuracy of our assay was comparable to both Sanger sequencing and the Xpert assay. Importantly, our assay boasts a 4.2-h turnaround time and costs only $10 per test, making it an optimal choice for peripheral healthcare settings.
CONCLUSION: These findings highlight our assay's potential as a promising tool for rapidly, accurately, and affordably detecting MDR-TB.

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PubMed Non-Open Access

36. Levofloxacin Preventive Treatment in Children Exposed to MDR Tuberculosis.

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BACKGROUND: Worldwide, approximately 2 million children younger than 15 years of age are infected with multidrug-resistant (MDR) Mycobacterium tuberculosis, with MDR tuberculosis developing in approximately 30,000 annually. Evidence from randomized, controlled trials on tuberculosis preventive treatment in persons exposed to MDR tuberculosis is lacking.
METHODS: In this community-based, multisite, double-blind, cluster-randomized, placebo-controlled trial in South Africa, we assessed the efficacy and safety of levofloxacin as preventive treatment in children with household exposure to an adult with bacteriologically confirmed MDR pulmonary tuberculosis. Children younger than 5 years of age were eligible for inclusion regardless of interferon-γ release assay result or human immunodeficiency virus (HIV) status, and children 5 to 17 years of age were eligible if they had a positive interferon-γ release assay or HIV infection. Households were randomly assigned to a trial regimen, and children in the household received levofloxacin or placebo once daily for 24 weeks. The primary efficacy end point was incident tuberculosis, which included death from tuberculosis, by week 48 after randomization. The primary safety end point was any adverse event of grade 3 or higher during the treatment period that was at least possibly related to the trial regimen.
RESULTS: Of 922 participants from 497 households, 453 were assigned to receive levofloxacin and 469 to placebo; 91.0% of the participants were younger than 5 years of age. At least 80% of the assigned doses of levofloxacin or placebo were received by 86% of the participants in each trial group. By week 48, tuberculosis had developed in 5 participants (1.1%) in the levofloxacin group

and in 12 participants (2.6%) in the placebo group (hazard ratio, 0.44; 95% confidence interval [CI], 0.15 to 1.25). The results of sensitivity analyses were consistent with those of the primary analysis. Grade 3 or higher adverse events during the treatment period that were considered to be at least possibly related to the trial regimen occurred in 4 participants in the levofloxacin group and in 8 participants in the placebo group (hazard ratio, 0.52; 95% CI, 0.16 to 1.71). Grade 2 tendonitis occurred in 1 child in the levofloxacin group. CONCLUSIONS: Although preventive treatment with levofloxacin led to a lower incidence of tuberculosis than placebo among children with household exposure to MDR tuberculosis, the difference was not significant. (Supported by Unitaid and others; TB-CHAMP ISRCTN Registry number, ISRCTN92634082.).

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37. Levofloxacin for the Prevention of Multidrug-Resistant Tuberculosis in Vietnam.

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BACKGROUND: Prevention of drug-resistant tuberculosis is a global health priority. However, trials evaluating the effectiveness of treating Mycobacterium tuberculosis infection among contacts of persons with drug-resistant tuberculosis are lacking.
METHODS: We conducted a double-blind, randomized, controlled trial comparing 6 months of daily levofloxacin (weight-based doses) with placebo to treat M. tuberculosis infection. The trial population comprised household contacts of persons with bacteriologically confirmed rifampicin-resistant or multidrug-resistant (MDR) tuberculosis in Vietnam. Contacts of any age with a positive tuberculin skin test or immunologic impairment were eligible. The primary end point was bacteriologically confirmed tuberculosis within 30 months. Secondary end points included grade 3 or 4 adverse events, death from any cause, and acquired drug resistance.
RESULTS: Of 3948 persons screened for eligibility, 61 (1.5%) had coprevalent tuberculosis (defined as active tuberculosis disease diagnosed before randomization) and 2041 underwent randomization. Of these 2041 participants, 1995 (97.7%) completed 30 months of follow-up, had a primary end-point event, or died. Confirmed tuberculosis occurred in 6 participants (0.6%) in the levofloxacin group and 11 (1.1%) in the placebo group (incidence rate ratio, 0.55; 95% confidence interval [CI], 0.19 to 1.62); this difference was not significant. There was little difference in grade 3 or 4 adverse events between the two groups (risk difference, 1.0 percentage point; 95% CI, -0.3 to 2.4). Adverse events of any grade were reported in 306 participants (31.9%) taking levofloxacin and 125 (13.0%) taking placebo (risk difference, 18.9 percentage points; 95% CI, 14.2 to 23.6). No acquired fluoroquinolone resistance was observed.
CONCLUSIONS: Although the incidence of tuberculosis was lower in the levofloxacin group than in the placebo group at 30 months, the difference was not significant. (Funded by the National Health and Medical Research Council of Australia; VQUIN MDR Australia New Zealand Clinical Trials Registry number, ACTRN12616000215426.).

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38. Executive summary: Clinical practice guidelines on the management of resistant tuberculosis of the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR) and the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC).

Enferm Infecc Microbiol Clin (Engl Ed). 2024 Dec;42(10):588-596. doi: 10.1016/j.eimce.2024.09.001.

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The Spanish Society of Pneumology and Thoracic Surgery (SEPAR) and the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC) have developed together Clinical Practice Guidelines (GPC) on the management of people affected by tuberculosis (TB) resistant to drugs with activity against Mycobacterium tuberculosis. These clinical practice guidelines include the latest updates of the SEPAR regulations for the diagnosis and treatment of drug-resistant TB from 2017 to 2020 as the starting point. The methodology included asking relevant clinical questions based on PICO methodology, a literature search focusing on each question, and a systematic and comprehensive evaluation of the evidence, with a summary of this evidence for each question. Finally, recommendations were developed and the level of evidence and the strength of each recommendation for each question were established in concordance with the GRADE approach. Of the recommendations made, it is worth highlighting the high quality of the existing evidence for the use of nucleic acid amplification techniques (rapid genotypic tests) as initial tests for the detection of the M. tuberculosis genome and rifampicin resistance in people with presumptive signs or symptoms of pulmonary TB; and for the use of an oral combination of anti-TB drugs based on bedaquiline, delamanid (pretomanid), and linezolid, with conditional fluoroquinolone supplementation (conditioned by fluoroquinolone resistance) for six months for the treatment of people affected by pulmonary multidrug-resistant tuberculosis (MDR-TB). We also recommend directly observed therapy (DOT) or video-observed treatment for the treatment of people affected by DR-TB.

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39. Spatial distribution and predictors of drug-resistant tuberculosis incidence in Mozambique: A nationwide Bayesian disease mapping study.

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INTRODUCTION: Mozambique is among the highest-burden countries for drug-resistant tuberculosis in the world. However, the spatial distribution of drug-resistant tuberculosis, in the country is unknown. Therefore, we aimed to analyse the spatial distribution, predictors, and hotspot districts for drug-resistant tuberculosis incidence in Mozambique.
METHOD: We carried out an ecological study using the district as the unit of analysis where we included all cases of drug-resistant tuberculosis diagnosed in Mozambique from 2016 to 2020. We obtained the data from the Minister of Health and other open sources. Parameters of interest were estimated through a spatial Bayesian Poisson regression model using Markov Chain Monte Carlo simulation.
RESULTS: A total of 5092 people with drug-resistant tuberculosis in Mozambique were diagnosed during our study period. We found heterogeneity in the spatial distribution of drug-resistant tuberculosis incidence across the country. Higher incidence rates were mainly observed in the south and central regions, and 26 (16.9%) districts out of 154 were identified as hotspot areas. The incidence of drug-resistant tuberculosis increased with an increase in the HIV prevalence (Relative risk [RR]: 1.53; 95% Credibility Interval [CrI]: 1.32 to 1.76),

electricity coverage rate (RR: 1.59; 95% CrI: 1.19 to 2.09), and population density (RR: 1.36; 95% CrI: 1.08 to 1.69) and decreased with an increase in the proportion of people with a bank account per district (RR: 0.71; 95% CrI: 0.51 to 0.96).
CONCLUSION: The incidence of drug-resistant tuberculosis was not homogeneous, and it was associated with social determinants of health. Targeting interventions in hotspot districts and addressing social determinants is crucial for tuberculosis elimination in Mozambique.

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PMID: 39587324 [Indexed for MEDLINE]

40. Examining effective monotherapy hypothesis for TB therapy failure and resistance emergence.

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<sec><title>BACKGROUND</title>We tested the hypothesis that because of the different metabolic states of Mycobacterium tuberculosis (Mtb) in lesions, drugs in combination therapy often act effectively as monotherapy, leading to therapy failure and resistance emergence.</sec><sec><title>METHODS</title>Bactericidal and sterilizing activity studies were performed in the hollow fiber system of TB (HFS-TB) using the human equivalent dose of isoniazid (INH) 300 mg/day, rifampin (RIF) 600 mg/day, and pyrazinamide (PZA) 1.5 g/day either as monotherapy, two-, and three-drug combination for 28 days. The Mtb population (log10 CFU/ml) for each drug, either monotherapy or combination, was compared using an analysis of variance.</sec><sec><title>RESULTS</title>In the bactericidal activity studies, the microbial kill was driven by INH, followed by RIF, and PZA monotherapy failed. During the sterilizing activity, INH and RIF displayed similar microbial kill. The INH + RIF and RIF + PZA combinations were significantly different from each other but not from the INH + RIF + PZA combination. RIF and INH-resistant subpopulations did not increase despite premixing the inoculum with

isogenic-resistant strains.</sec><sec><title>CONCLUSION</title>Effective monotherapy arising from the selectivity of antibiotics against special Mtb sub-populations may not be the primary mechanism of resistance emergence. Different metabolic populations of Mtb were killed by more than one drug and were not under monotherapy when combination therapy was administered.</sec>.

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41. Insights to the role of phytoconstituents in aiding multi drug resistance - Tuberculosis treatment strategies.

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Multidrug resistant tuberculosis (MDR-TB) have emerged as a global challenge. There are several underlying mechanisms which are involved in causing mycobacterial resistance towards antitubercular agents including post translational modifications, efflux pumps and gene mutations. This resistance necessitates the investigation of complementary therapeutic options including the use of bioactive compounds from plants. Recent studies have focused on recognising and isolating the characteristics of these compounds to assess their potential against MDR-TB. Phytoconstituents such as alkaloids, flavonoids, terpenoids, glycosides, and essential oils have shown promising antimicrobial activity against Mycobacterium tuberculosis. These compounds can either directly kill or inhibit the growth of M. tuberculosis or enhance the immune system's ability to fight against the infection. Some studies suggest that combining phytoconstituents with standard antitubercular medications works synergistically by enhancing the efficacy of drug, potentially lowering the associated risk of side effects and eventually combating resistance development. This review attempts to elucidate the potential of phytoconstituents in combating resistance in MDR-TB which hold a promise to change the course of treatment strategies in

tuberculosis.

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42. Identification of novel DNA gyrase inhibitor by combined pharmacophore modeling, QSAR analysis, molecular docking, molecular dynamics, ADMET and DFT approaches.

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DNA gyrase, an ATP-dependent enzyme, plays a critical role in DNA replication, transcription, and recombination in Mycobacterium tuberculosis (MTB). While fluoroquinolones are effective antibacterial agents targeting DNA gyrase, their clinical use is often limited due to side effects and the emergence of bacterial resistance. In this study, we developed a quantitative structure-activity

relationship (QSAR) model to predict the anti-tubercular activity of Quinoline-Aminopiperidine derivatives targeting the DNA gyrase enzyme, using a dataset of 48 compounds obtained from the literature. The QSAR model was validated using both internal and external validation metrics. Model 4, the best predictive model, demonstrated a strong fit with an R^2 of 0.8393, an adjusted R^2 (R^2adj) of 0.8010, and a lack of fit (LOF) parameter of 0.0626. The QSAR results revealed that DNA gyrase inhibition is significantly influenced by factors such as partition coefficient, molecular flexibility, hydrogen bonding potential, and the presence of fluorine atoms. Twelve quinoline-aminopiperidine derivatives were designed, and their anti-tubercular activity was predicted using QSAR model-4. These compounds were further assessed for pharmacokinetic properties, toxicity, and binding affinity to DNA gyrase. Pharmacophore modeling was also performed and validated using MOE software. The final pharmacophore model includes the features of two aromatic hydrophobic features, one hydrogen bond acceptor, and one hydrogen bond donor. The results indicated that designed compounds QA-3 and dataset compounds C-34 exhibit favorable drug-likeness properties. Molecular dynamics simulations confirmed the stable binding of compounds QA-3 and C-34 to the DNA gyrase protein, highlighting their potential as promising anti-tubercular agents. The developed QSAR Model-4 will facilitate the prediction of anti-tubercular activity in Quinoline-Aminopiperidine derivatives.

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43. Advancements and challenges in tuberculosis drug discovery: A comprehensive overview.

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Tuberculosis continues to pose a health challenge causing the loss of millions of lives despite the existence of multiple drugs, for treatment. The emergence of drug-resistant strains has made the situation more complex making it increasingly difficult to fight against this disease. This review outlines the challenges associated with TB drug discovery, the nature of Mycobacterium tuberculosis shedding light on the mechanisms that lead to treatment failure and antibiotic resistance. We explore promising drug targets, encompassing inhibition of mycolyarabinogalactan peptidoglycan (MAGP) assembly, mycolic acid biosynthesis, DNA replication, transcription, translation, protein synthesis, and bioenergetics/metabolism pathways. A comprehensive overview of the global pipeline of anti-tuberculosis drugs at various stages of clinical trials, the diverse strategies being pursued to tackle this complex disease. By gaining an understanding of the mechanisms that contribute to resistance development and identifying suitable targets, we can pave the way for more effective treatments and contribute to global efforts to combat drug-resistant tuberculosis.

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44. Quinoline hybrid derivatives as effective structural motifs in the treatment of tuberculosis: Emphasis on structure-activity relationships.

Tuberculosis (Edinb). 2024 Dec;149:102573. doi: 10.1016/j.tube.2024.102573. Epub 2024 Nov 3.

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Mycobacterium tuberculosis (MTB/Mtb) is the causative agent of tuberculosis (TB), a highly infectious serious airborne illness. TB usually affects the lungs, in 25 % of patients (children or immune impaired adults), mycobacteria can enter the blood stream and infect other bodily areas such the meninges, pleura, lymphatic system, genitourinary system, bones, and joints. Currently, the most challenging aspect of treating this illness is the ineffectiveness of the most potent first-line anti-TB medications, isoniazid, rifampin, pyrazinamide, and ethambutol, which can result in multidrug-resistant TB (MDR-TB), extensively drug-resistant TB (XDR-TB), and in rare instances, completely drug-resistant TB (TDR-TB). As a result, finding new pharmaceutical compounds to treat these diseases is a significant challenge for the scientific community. A number of bio-active molecules have been investigated in this quest, including quinoline, which is considered a promising candidate for the development of TB drugs. It is known that quinoline are low in toxicity and have a wide range of pharmacological properties. Researchers have investigated quinoline scaffolds as anti-TB drugs based on their biological spectrum. The objective of this review is to examine the recent development of quinoline and its structural characteristics crucial to its antitubercular (anti-TB) activity. A molecular analog of the TB treatment can be designed and identified with this information. As a result, future generation quinoline-based anti-TB agents with greater potency and safety can also be explored.

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45. Analysis of genetic characteristics associated with reduced bedaquiline susceptibility in multidrug-resistant Mycobacterium tuberculosis.

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Bedaquiline (BDQ) has shown efficacy in shortening treatment duration and enhancing treatment success rates for multidrug-resistant tuberculosis (MDR-TB), thereby prompting widespread adoption. However, resistance to BDQ has emerged. This study aimed to identify genetic characteristics associated with decreased susceptibility to BDQ, using a public database to aid in the detection of resistant strains. Seventy-one BDQ-resistant and 929 BDQ-susceptible isolates from the open-source CRyPTIC database were selected for analysis. Variant calling was conducted via the clockwork pipeline. Univariate logistic regression was performed for each gene mutation, followed by LASSO regression for further variant selection. Ultimately, a multiple linear regression model was developed using log2-transformed Minimum Inhibitory Concentration values as the dependent variable, with variant selection refined through stepwise regression based on the Akaike Information Criterion. Ten gene mutations were significantly associated with reduced BDQ susceptibility, including two key gene mutations: Rv0678_141_ins_1 and Rv1979c_D249E, with effect estimates of 1.76 (95 % CI: 0.67-2.84) and 1.69 (95 % CI: 0.22-3.17), respectively. Other implicated genes included Rv2699c_-84_del_1, hsaB_I179T, mmpL9_T241A, pncA_C14R, Rv0373c_G621S, Rv0893c_L27F, Rv1770_A4D, and Rv3428c_S327C. This study identified ten gene mutations linked to decreased susceptibility to BDQ, providing a reference for developing a comprehensive catalog of BDQ-resistant genes.

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46. Drug repurposing: An antidiabetic drug Ipragliflozin as Mycobacterium tuberculosis sirtuin-like protein inhibitor that synergizes with anti-tuberculosis drug isoniazid.

Int J Biol Macromol. 2024 Dec;282(Pt 3):137003. doi: 10.1016/j.ijbiomac.2024.137003. Epub 2024 Oct 29.

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The surge of drug-resistant Mycobacterium tuberculosis (DR-TB) impedes the World Health Organization's efforts in ending TB and calls for new therapeutic formulations. M. tuberculosis sirtuin-like protein Rv1151c is a bifunctional enzyme with both deacetylation and desuccinylation activities, which plays an important role in M. tuberculosis drug resistance and stress responses. Thus, it appears to be a promising target for the development of new TB therapeutics. In this study, we screened 31,057 ligand compounds from seven compound libraries in silico to identify inhibitors of Rv1151c. Ipragliflozin can bind to Rv1151c and interact stably. Ipragliflozin can change the acylation level of M. tuberculosis by inhibiting Rv1151c and effectively inhibit the growth of M. tuberculosis H37Rv and M. smegmatis. It can potentiate the first-front anti-TB drug isoniazid. As an antidiabetic drug, Ipragliflozin can be potentially included in the regimen to treat diabetes-tuberculosis comorbidity.

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47. Mycobacterium tuberculosis inhibitors: an updated patent review (2021-present).

Expert Opin Ther Pat. 2024 Dec;34(12):1215-1230. doi: 10.1080/13543776.2024.2419826. Epub 2024 Nov 18.

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INTRODUCTION: Tuberculosis (TB) remains a major global health issue, causing around 10 million new cases and 1.3 million deaths in 2022. The challenge is compounded by multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB strains, and co-infection with HIV.
AREAS COVERED: The present review examines significant patent literature on TB chemotherapeutics from September 2021 to the present using the following databases, reaxys, google patent and espacenet. Only patents reporting compounds with a minimum inhibitory concentration (MIC) on whole Mycobacterium tuberculosis cells of ≤5 μM were selected for review.
EXPERT OPINION: The fight against TB is advancing with the development of promising new compounds due to the challenge of drug-resistant strains. Notable among those reviewed in this paper are the benzothiazinones, showing high efficacy against both drug-sensitive and resistant TB strains. Additionally, Q203 analogues, demonstrate strong antitubercular activity, good microsomal stability, and favorable safety profiles. Finally, LysRS inhibitors also show significant promise in vivo models. These advancements underscore the importance of novel targets and innovative strategies in developing effective, resistance-resistant TB treatments.

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PMID: 39431728 [Indexed for MEDLINE]

48. 3,5-disubstituted pyridines with potent activity against drug-resistant Mycobacterium tuberculosis clinical isolates.

Future Med Chem. 2024;16(22):2351-2369. doi: 10.1080/17568919.2024.2403963. Epub 2024 Oct 3.

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

Plain Language Summary: [Box: see text].

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

Curr Mol Pharmacol. 2024;17:e18761429314641. doi: 10.2174/0118761429314641240815080447.

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

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PMID: 39317997 [Indexed for MEDLINE]

50. Epidemiologic characteristics and risk factors of Clostridioides difficile infection in patients with active tuberculosis in the Republic of Korea: a nationwide population-based study.

J Hosp Infect. 2024 Dec;154:1-8. doi: 10.1016/j.jhin.2024.07.019. Epub 2024 Sep 13.

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BACKGROUND: The relationship between anti-tuberculosis (TB) agents and Clostridioides difficile infection (CDI) remains unclear. This study aimed to investigate the epidemiological characteristics and risk factors for CDI in patients with TB.
METHODS: This nationwide, population-based cohort study was conducted in the Republic of Korea (ROK) between January 2018 and December 2022. Data were extracted from the National Health Insurance Service-National Health Information Database. The risk factors for CDI in patients with TB were identified through multi-variate logistic regression analysis using a 1:4 greedy matching method based on age and sex.
RESULTS: During the study period, CDI developed in 2901 of the 131,950 patients with TB who were prescribed anti-TB agents. The incidence of CDI in patients with TB has increased annually in the ROK from 12.31/1000 in 2018 to 33.51/1000 in 2022. Oral metronidazole (81.94%) was the most common first-line treatment for CDI. The in-hospital mortality rate of patients with concomitant CDI and TB was 9.9%, compared with 6.9% in those with TB alone (P<0.0001). Multi-variate logistic regression analysis found intensive care unit admission, Charlson Comorbidity Index ≥3, antibiotic exposure, standard regimen, multi-drug-resistant TB and extrapulmonary TB to be significant risk factors for development of CDI in patients with TB.
CONCLUSION: CDI is uncommon in patients with TB, but it results in a significantly increased mortality rate. Patients being treated for TB should be monitored carefully for the development of CDI. Further clinical research is warranted to identify effective interventions for preventing and controlling CDI during TB treatment.

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PMID: 39278268 [Indexed for MEDLINE]

51. Increasing circulation of multi-drug resistant tuberculosis strains in Buryatia, high-burden and ethnically diverse region in the Russian Far East.

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Buryatia is a multidrug-resistant tuberculosis (MDR-TB) high-burden region in the Russian Far East with ethnically diverse population (30 % Mongoloid Buryats and 65 % Russians). Two hundred M. tuberculosis strains from newly-diagnosed patients were subjected to phenotypic testing and genotyping. The Beijing genotype was more prevalent among Russians than Buryats (68 % vs 53 %; P = 0.055). European non-Beijing genotypes (LAM, Ural, Haarlem) were double more prevalent in Buryats vs Russians (39.2 % vs 20.5 %; P = 0.01). Higher prevalence of Beijing among former prison inmates (79 % vs 61 % in other patients, P = 0.1) suggests its increased transmissibility. The Russian epidemic cluster B0/W148 was in 9.5 %, double smaller than elsewhere in Siberia. The hypervirulent Beijing 14717-15-cluster was endemic in Buryatia but paradoxically enough, it was more frequently isolated from Russians than Buryats (9.1 % vs 3.9 %; P = 0.2). Beijing subtypes B0/W148, CAO, and 14717-15 were associated with poly/multi-drug resistance (P = 0.01-0.0001). HIV coinfection was more frequent in Russians than in Buryats: 35/141 (24.8 %) vs 5/51 (9.8 %), P = 0.03. To conclude, M. tuberculosis population structure in Buryatia retained its singularities compared to other parts of Russia and remains strikingly different from the neighboring Mongolia. A circulation of strongly MDR-associated Beijing subtypes and drug-resistant non-Beijing strains highlights a risk of their broader dissemination.

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52. Effectiveness and Safety of Varying Doses of Linezolid With Bedaquiline and Pretomanid in Treatment of Drug-Resistant Pulmonary Tuberculosis: Open-Label, Randomized Clinical Trial.

Clin Infect Dis. 2024 Dec 17;79(6):1375-1385. doi: 10.1093/cid/ciae388.

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BACKGROUND: Treatment of drug-resistant tuberculosis with bedaquiline-pretomanid-linezolid regimen has demonstrated good treatment efficacy. Given linezolid's toxicity profile, prudence suggests reconsidering its dose and duration. We determined the effectiveness and safety of structured dose reduction of linezolid with bedaquiline and pretomanid in adults with pre-extensively drug-resistant (pre-XDR) or treatment-intolerant/nonresponsive multidrug-resistant (MDRTI/NR) pulmonary tuberculosis.
METHOD: Adults with pre-XDR or MDRTI/NR pulmonary tuberculosis were enrolled in a multicenter, parallel-group, randomized clinical trial in India. Patients were randomized to 26 weeks of bedaquiline, pretomanid, and daily linezolid, at 600 mg for 26 weeks (arm 1); 600 mg for 9 weeks followed by 300 mg for 17 weeks (arm 2); or 600 mg for 13 weeks followed by 300 mg for 13 weeks (arm 3). Study end points included sustained cure, bacteriological failure, toxicity, and death.
RESULTS: Of 403 patients enrolled, 255 (63%) were <30 years old, 273 (68%) had prior tuberculosis episodes, and 238 (59%) were malnourished. At the end of treatment, after excluding those with negative baseline cultures, cure was seen in 120 (93%), 117 (94%), and 115 (93%) in arms 1, 2, and 3 respectively. Myelosuppression seen in 85 patients each in arms 1 and 2 and 77 patients in arm 3, not significantly different. Peripheral neuropathy was noticed in 66 patients (30, 17, and 19 in arms 1, 2, and 3) at 10-26 weeks (P = .02). The linezolid dose was reduced because of toxicity in 13, 2, and 4 patients in arms 1, 2, and 3, respectively.
CONCLUSIONS: In adults with pre-XDR or MDRTI/NR pulmonary tuberculosis, structured linezolid dose reduction to 300 mg/d is as effective as the standard 600-mg dose but with fewer cases of peripheral neuropathy when given with bedaquiline and pretomanid.
CLINICAL TRIALS REGISTRATION: Clinical Trial Registry of India (CTRI/2021/03/032189).

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

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PURPOSE: To assess the Xpert MTB/XDR assay's efficiency in promptly detecting resistance to isoniazid, fluoroquinolones, ethionamide, and second-line injectable drugs among tuberculosis (TB) patients.
METHODS: From August 2020 to July 2021, TB suspected patient samples were enrolled at a tertiary care center for our study. We conducted mycobacterial culture, phenotypic DST using proportion method in liquid culture at WHO-recommended concentrations, and the line probe assay (LPA). Simultaneously, the Index test, Xpert MTB/XDR, was performed following the manufacturer's

instructions.
RESULTS: Among 360 samples, 107 were excluded due to incomplete information. Resistance to isoniazid, levofloxacin and moxifloxacin was found in 45/251, 21/251 and 20/251 samples, respectively by phenotypic DST. The diagnostic accuracy of Index test, taking phenotypic DST as a reference standard, was 95.8%, 99.04%, and 99.05% for isoniazid, levofloxacin, and moxifloxacin, respectively. The Index test assay demonstrated a specificity of 99.1% for detecting SLID resistance, yielding a diagnostic accuracy of 99.2. Comparing the Index test with LPA revealed a significant enhancement in sensitivity for detecting isoniazid resistance (86.7% vs. 82.2%).
CONCLUSIONS: The Index test exhibited promising outcomes in identifying resistance to isoniazid and fluoroquinolones, surpassing the performance of the LPA. This could be valuable for promptly initiating treatment in cases of drug-resistant tuberculosis.

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54. Mycobacterial FtsZ and inhibitors: a promising target for the anti-tubercular drug development.

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The emergence of multidrug-resistant tuberculosis (MDR-TB) strains has rendered many anti-TB drugs ineffective. Consequently, there is an urgent need to identify new drug targets against Mycobacterium tuberculosis (Mtb). Filament Forming Temperature Sensitive Gene Z (FtsZ), a member of the cytoskeletal protein family, plays a vital role in cell division by forming a cytokinetic ring at the cell's center and coordinating the division machinery. When FtsZ is depleted, cells are unable to divide and instead elongate into filamentous structures that eventually undergo lysis. Since the inactivation of FtsZ or alterations in its assembly impede the formation of the Z-ring and septum, FtsZ shows promise as a target for the development of anti-mycobacterial drugs. This review not only discusses the potential role of FtsZ as a promising pharmacological target for anti-tuberculosis therapies but also explores the structural and functional aspects of the mycobacterial protein FtsZ in cell division. Additionally, it reviews various inhibitors of Mtb FtsZ. By understanding the importance of FtsZ in cell division, researchers can explore strategies to disrupt its function, impeding the growth and proliferation of Mtb. Furthermore, the investigation of different inhibitors that target Mtb FtsZ expands the potential for developing effective treatments against tuberculosis.

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Tb News

1. **J&J denied extension of patent on TB drug, to benefit patients**

   https://timesofindia.indiatimes.com/india/jj-denied-extension-of-patent-on-tb-drug-to-benefit-patients/articleshow/116383276.cms

This month, the Indian Patent Office denied the last of the three Janssen patent extension applications for bedaquiline. While TB treatment is generally covered by the Indian government, long acting injectables are not, making the long acting version of bedaquiline inaccessible to millions. This final ruling will allow for the continued expansion of access to treatment across the country.

2. **Children at Risk of Multidrug-Resistant TB Get Prevention Option**

   https://www.bnnbloomberg.ca/business/company-news/2024/12/18/children-at-risk-of-multidrug-resistant-tb-get-prevention-option/

   The results of the TB-CHAMP trial were recently published. They showed that prophylactic levofloxacin can significantly reduce the risk of contracting MDR-TB in children younger than 5 who had a household exposure. This is one of the first successful trials for prevention of MDR-TB.

3. **UN health agency approves 'groundbreaking' TB test**

   https://news.un.org/en/story/2024/12/1157806

   The Xpert MTB/RIF ultra test achieved prequalification status from the UN this month. This will allow the test to be purchased by governments and UN agencies. The salivary test can provide diagnostic results and identify first line resistance within hours.