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

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OBJECTIVES: Whole-genome sequencing (WGS) was employed to investigate antibiotic resistance, virulence and transmission profiles of multidrug-resistant tuberculosis (MDR-TB) isolates from Shanghai, China.
METHODS: A total of 306 MDR-TB clinical isolates were collected from Shanghai Pulmonary Hospital and underwent phenotypic drug susceptibility testing (DST) for common anti-TB drugs and WGS. Combined 778 published bacterial sequences, we performed phylogenetic analysis, resistance and virulence gene identification to understand the genetic relationships and resistance mechanisms among those strains.
RESULTS: WGS determination, supported by DST, revealed high resistance rates for isoniazid (83.66%) and rifampicin (90.20%) among the MDR-TB isolates. Key resistance-associated mutations included katG Ser315Thr for isoniazid, rpoB mutations for rifampicin, and embB Met306Val for ethambutol. WGS demonstrated >90% concordance with culture-based DST for most drugs, except ethambutol that showed a 76.80% concordance. Analyses of virulence factors and phylogenetics revealed the genetically homogeneous, endemic MDR-TB population in Shanghai, with no evidence of recent transmission.
CONCLUSIONS: This study highlights the genetic homogeneity and endemic nature of MDR-TB in Shanghai, providing insights into key resistance mechanisms of TB.

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2. Multi-drug resistance and compensatory mutations in Mycobacterium tuberculosis in Vietnam.

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BACKGROUND: Vietnam is a hotspot for the emergence and spread of multidrug-resistant Mycobacterium tuberculosis. This study aimed to perform a retrospective study on the compensatory evolution in multidrug-resistant M. tuberculosis strains and the association with drug-resistant mutations and M. tuberculosis genotypes.
METHODS: Hundred and seventy-three strains resistant to rifampicin (n = 126) and/or isoniazid (n = 170) (multidrug-resistant = 123) were selected according to different drug-resistant patterns and genotypes. The genes/promoter regions including rpoA, rpoB, rpoC, katG, inhA, inhA promoter, ahpC, ahpC promoter, gyrA, gyrB, and rrs were sequenced for each strain.
RESULTS: Frequency of rifampicin- and isoniazid-resistant mutations in multidrug-resistant strains was 99.2% and 97.0%, respectively. Mutations associated with low -high levels of drug resistance with low- or no-fitness costs compared to the wild type, including rpoB_Ser450Leu, katG_Ser315Thr, inhA-15(A-T), gyrA_Asp94Gly, and rrs_A1401GA, accounted for 46.3%, 76.4%, 16.2%, 8.9%, and 11.4%, respectively, in the multidrug-resistant strains. Beijing and Euro-American genotype strains were associated with high-level drug-resistant mutations, rpoB_Ser450Leu, katG_Ser315Thr, and gyrA_Asp94Gly, while East African-Indian genotype strains were associated with low to high-level

drug-resistant mutations, rpoB_His445Asp, rpoB_His445Tyr, inhA-15(C-T) and rrs_A1401G. Multidrug-resistant strains (19.5%) harboured compensatory mutations linked to rifampicin resistance in rpoA, rpoB, or rpoC. Notably, the frequency of compensatory mutations in Beijing genotypes was significantly higher than in East African-Indian genotypes (21.1% vs. 3.3%, OR = 7.7; 95% CI = 1.0 to 61.2, p = 0.03). The proportion of multidrug-resistant strains with rpoB_Ser450Leu mutations carrying rpoA-rpoC mutations was higher than that of strains with other rpoB mutations (OR = 5.4; 95% CI = 1.4 to 21.1, p = 0.02) and was associated with Beijing strains. Only 1.2% (2/170) isoniazid-resistant strains carried aphC-52(C-T) mutation in the promoter region of the ahpC gene, which was hypothesised to be the compensatory mutation in isoniazid-resistant strains. Meanwhile, 11 isoniazid-resistant strains carried a katG mutation combined with either inhA-8(T-C) or inhA-15(A-T) mutations and were associated with East African-Indian strains.
CONCLUSIONS: Mutations associated with high levels of drug resistance without/with low fitness costs (rpoB_Ser450Leu and katG_Ser315Thr) along with compensatory mutations linked to rifampicin resistance were strongly associated with multidrug-resistant M. tuberculosis Beijing strains in Vietnam.

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3.Second-line drug resistance among multidrug-resistant tuberculosis patients in Ethiopia: A laboratory-based surveillance.

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OBJECTIVES: To estimate the proportion of second-line anti-tuberculosis drug resistance among multidrug-resistant tuberculosis (MDR-TB) patients in Ethiopia.
METHODOLOGY: A laboratory-based prospective cross-sectional study was conducted at the National Tuberculosis Reference Laboratory (NTRL), Ethiopia, from February 2022 to July 2024. Phenotypic drug susceptibility testing (pDST) assessed resistance to various second-line antituberculosis drugs. The collected data were entered into Microsoft Excel 2016 and imported into Statistical Package for Social Sciences (SPSS) version 23 for descriptive analysis.
RESULT: Of 468 MDR-TB patients, 262 were new, and 206 were previously treated cases. Pre-extensively drug-resistant tuberculosis (pre-XDR-TB) was identified in four (1.52%) new cases and seven (3.40%) previously treated cases. Extensively drug-resistant tuberculosis (XDR-TB) was detected in three (1.15%) new cases and two (0.97%) previously treated cases. Overall, 11 (2.35%) cases were classified as pre-XDR-TB, and five (1.07%) as XDR-TB. Combined resistance to fluoroquinolones (FQs) and bedaquiline were detected in four cases (0.85%), comprising three new cases (1.15%) and one previously treated case (0.49%). Resistance to both FQs and linezolid was detected in a single previously treated case (0.49%) and acquired resistance to second-line drugs was identified in four cases.
CONCLUSIONS: Our study showed a prevalence of 2.35% for pre-XDR-TB and 1.07% for XDR-TB among MDR-TB cases, highlighting the importance of continuous surveillance and tailored treatment approaches to control the spread of drug-resistant TB (DR-TB) in Ethiopia. Future studies on MDR-TB surveillance should prioritize the integration of genomic surveillance into routine laboratory-based DR-TB monitoring systems to enhance early detection of resistance patterns, support targeted treatment strategies, and improve overall patient management efforts.

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4. Phenotypic drug susceptibility testing for Mycobacterium tuberculosis variant bovis BCG in 12 hours.

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Drug-resistant tuberculosis (DR-TB) kills ~200,000 people every year. A contributing factor is the slow turnaround time (TAT) associated with drug susceptibility diagnostics. The prevailing gold standard for phenotypic drug susceptibility testing (pDST) takes at least two weeks. Here we show that growth-based pDST for slow-growing mycobacteria can be conducted in 12 h. We use Mycobacterium tuberculosis variant bovis Bacillus Calmette-Guérin (BCG) and Mycobacterium smegmatis as the mycobacterial pathogen models and expose them to antibiotics used in (multidrug-resistant) tuberculosis (TB) treatment regimens - i.e., rifampicin (RIF), isoniazid (INH), ethambutol (EMB), linezolid (LZD), streptomycin (STR), bedaquiline (BDQ), and levofloxacin (LFX). The bacterial growth in a microfluidic chip is tracked by time-lapse phase-contrast microscopy. A deep neural network-based segmentation algorithm is used to quantify the growth rate and to determine how the strains responded to drug treatments. Most importantly, a panel of susceptible and resistant M. bovis BCG are tested at critical concentrations for INH, RIF, STR, and LFX. The susceptible strains could be identified in less than 12 h. These findings are comparable to what we expect for pathogenic M. tuberculosis as they share 99.96% genetic identity.

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interests.

5. Prevalence of bedaquiline resistance in patients with drug-resistant tuberculosis: a systematic review and meta-analysis.

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BACKGROUND: Drug-resistant tuberculosis (TB) remains a major global public health challenge. While bedaquiline (BDQ) offers improved treatment outcomes for patients with multi-drug resistant TB (MDR-TB), its widespread use has led to the emergence of BDQ resistance.
METHODS: This systematic review evaluated the prevalence of BDQ resistance among adult patients through searches of PubMed, Web of Science, and Embase databases. Sensitivity and subgroup analyses were performed to explore sources of heterogeneity and compare prevalence estimates across groups. The Joanna Briggs Institute's quality assessment checklist was used to evaluate the methodological quality of the included studies. Heterogeneity between studies was evaluated using Cochran's Q and I2 tests.This study is registered with PROSPERO, CRD42024620791.
RESULTS: The weighted average prevalence of BDQ resistance was 5.7% (95% CI: 3.6-8.3), with acquired resistance reported at 5.4%. Geographic differences were observed, with South Africa showing a higher prevalence (10.4%) compared to China (2.4%).High-quality studies reported a prevalence of 5.2%, while fair-quality studies reported 7.7%. Mutations in the Rv0678 gene represented a significant proportion, reaching as high as 65.6%.
CONCLUSIONS: Our findings highlight an increasing trend in acquired resistance to BDQ, offering critical insights for managing MDR-TB. The application of whole-genome sequencing shows promise for advancing understanding of drug resistance mechanisms in Mycobacterium tuberculosis.

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6. A roadmap for integrating nutritional assessment, counselling, and support into the care of people with tuberculosis.

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Undernutrition-the leading risk factor for tuberculosis worldwide-is associated with impaired immunity, more extensive disease, delayed sputum conversion, and worse treatment outcomes, including mortality. In this Health Policy, we propose a comprehensive roadmap for integrating nutritional assessment, counselling, and support into tuberculosis treatment as part of person-centred care. At treatment initiation, we recommend standard nutritional assessment with anthropometric measurements and haemoglobin estimation, in addition to macronutrient and micronutrient support alongside nutritional counselling. Weight should be monitored during treatment and lack of weight gain at the end of the intensive phase should prompt an investigation of causes, such as food insecurity, poor treatment adherence, malabsorption, uncontrolled diabetes, or drug resistance. At the end of treatment, we recommend reassessing anthropometric measures to assess nutritional recovery. People with tuberculosis who remain underweight should receive close follow-up to detect early relapse. We call for annual reporting of nutritional metrics by WHO, explicit inclusion of nutritional assessment and care in national strategic plans, domestic or international support of nutritional programmes for people with tuberculosis, increased support for operational research initiatives, and integration of nutritional care into the WHO Multisectoral Accountability Framework at national and regional levels.

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assays for micronutrient status, based partially on technology developed in his research laboratory at Cornell University. All other authors declare no competing interests.

7. Genotypic analysis of drug-resistant tuberculosis in Ghana: Insights into pre-XDR and XDR-TB.

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BACKGROUND: The emergence of Extensively Drug Resistant (XDR) and Pre-extensively drug resistant (Pre-XDR) tuberculosis (TB) threatens the management of multidrug-resistant tuberculosis (MDR) patients and impacts negatively on TB control programs, especially in developing countries like Ghana. The first case of XDR-TB in Ghana was reported in 2018. There is however inadequate data on the burden of XDR-TB and pre-XDR-TB and their associated resistant mutations in Ghana. The study sought to provide baseline data on the burden of pre-XDR-TB and XDR-TB among MDR TB cases in Ghana. It also determined the mutations responsible for pre-XDR/ XDR-TB, for clinical and programmatic management of pre-XDR/ XDR-TB in Ghana.
METHODS: One hundred and seventy-one (171) archived clinical MDR isolates obtained from TB patients across Ghana between January 2016 and December 2020 were retrieved. The isolates were retested to confirm their phenotypic and genotypic susceptibility to the first and second-line anti-TB drugs using the BACTEC MGIT system and Genotype MTBDRplus, MTBDRsl, line probe assays respectively.
RESULTS: Most of the 171 isolates came from 7 regions; the highest (39.5%) from Eastern, followed by Greater Accra region (19.8%). Most of the isolates were from male TB patients (78.9%). Of the 171 archived isolates, 81 (47.4%) were confirmed to be MDR, 6 (7.4%) were Pre-XDR-TB but no XDR-TB was detected. The

katG S315T1 (33, 73.3%) and rpoB S531L (31, 42.5%) were the predominant mutations observed among isoniazid and rifampicin resistant isolates respectively. Many of the mutations and amino acid changes that caused pre-XDR-TB were gyrAWT3 + gyrAMUT3A and gyrAMUT3A (D94A) (50%) for fluoroquinolone. The other detected mutations with their amino acid changes were gyrA MUT1 (A90V), gyrAWT3 + gyrA MUT3C (D94G) and gyrA MUT2 (S91P) (16.7%) for fluoroquinolones and rrWT2 (position 1484) (33.3%) and rrs MUT2 (G1484T) (16.7%) for aminoglycosides.
CONCLUSION: The predominant mutations associated with pre-XDR-TB were D94A and C1402T for fluoroquinolone and aminoglycosides resistance respectively. The proportion of pre-XDR-TB among MDR-TB patients in Ghana was 7.4%; however, no XDR-TB was detected. A sustained surveillance of pre-XDR-TB and XDR-TB is recommended.

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8. Study protocol for a duration-randomized clinical trial to determine the optimal length of treatment for multidrug-resistant tuberculosis with a 5-drug regimen: The DRAMATIC trial.

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BACKGROUND: Current guidelines for the treatment of multidrug-resistant/rifampin-resistant tuberculosis (MDR/RR-TB) are based on clinical trials evaluating fixed duration regimens. However, when a regimen succeeds, it remains unknown whether a shorter duration could yield the same results. Similarly, if a regimen fails, it is unclear whether extending the treatment could improve outcomes. Trials are needed to assess the relationship between various treatment durations and outcomes.
METHODS/DESIGN: We designed a duration-randomized trial of treatment for fluoroquinolone-susceptible MDR/RR-TB. The DRAMATIC (Duration Randomized Anti-MDR-TB And Tailored Intervention Clinical) Trial is a multicenter, randomized, partially blinded, four-arm, phase 2 trial that examines an all oral, pyrazinamide-free regimen of bedaquiline, clofazimine, delamanid, linezolid, and levofloxacin, with administration of linezolid only in the initial 16 weeks of treatment. The four trial arms are treatment durations of 16, 24, 32 and 40 weeks. Randomization is stratified by "extensive" or "non-extensive" disease based on baseline smear (or Xpert) and cavitary status. The primary endpoint is relapse-free survival at week 76. The target sample size is 220. Participants are being enrolled in sites in the Philippines and Vietnam. The expected output will be an equation describing the relationship between treatment duration and the proportion of participants with relapse-free survival.
DISCUSSION: This trial aims to demonstrate that a duration-response relationship can be described for the treatment of MDR/RR-TB by a duration-randomized trial.

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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.

9. Tuberculosis among young contacts of patients with multidrug-resistant pulmonary tuberculosis in a reference hospital.

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OBJECTIVES: Young contacts of pulmonary tuberculosis (TB) patients face a higher risk of TB. Still, few studies have evaluated this risk among contacts of patients with pulmonary multidrug-resistant tuberculosis (MDR-TB). This study aimed to describe the incidence rate and the prevalence of TB infection (TBI) and TB disease (TBD) in young contacts of patients with MDR-TB.
METHODS: The authors retrospectively evaluated contacts of patients with pulmonary TB aged 0 to 19 for TBI and TBD in Rio de Janeiro between 2006 and 2016. Based on the drug susceptibility pattern and/or therapeutic regimen of the index case, contacts were classified into MDR-TB and non-MDR-TB contacts. A tuberculin skin test ≥ 5 mm was considered positive. Preventive therapy with isoniazid was offered to eligible contacts. Bivariate and multivariate logistic regressions estimated factors associated with TBI.
RESULTS: 439 contacts were screened; 129 were MDR-TB and 310 were non-MDR-TB contacts. TBI prevalence was 68.2 % in MDR-TB vs. 61.9 % in non-MDR-TB contacts ($p = 0.23$). Tuberculin conversion was higher among MDR-TB contacts (45.5 % vs. 17.1 %; $p = 0.04$). TBD incidence rate was 47.7 in non-MDR-TB and 179.6 per 100,000 person-months in MDR-TB contacts ($p = 0.65$), for a total TBD prevalence of 2.5 %. The overall TPT completion rate was 67.2 %; 71.5 % in non-MDR-TB and 59 % in MDR-TB contacts ($p = 0.04$).
CONCLUSION: The authors identified a high prevalence of TBI among contacts of pulmonary MDR-TB and non-MDR-TB patients, with a higher tuberculin conversion rate in MDR-TB contacts, highlighting the urgency of effective TPT regimens for young contacts of patients with pulmonary MDR-TB.

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

10. Frailty modelling for multidrug-resistant tuberculosis mortality in Namibia.

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BACKGROUND: Multidrug-Resistant Tuberculosis (MDR-TB) is fast becoming a major public health concern, with 80% of the reported global MDR-TB deaths occurring in high burden countries including Namibia where drug susceptibility testing is not routinely performed. Previous studies on TB in Namibia have primarily focused on TB and HIV co-infection and MDR-TB development. However, no study to date has specifically examined the epidemiology of MDR-TB mortality or its associated risk factors at a national level. Thus, this study aimed at examining the variation of mortality among MDR-TB patients in Namibia and identifying its risk factors.
DESIGN AND METHODS: The study adopted a retrospective cohort study design using the 2014-2017 MDR-TB records, and a Gompertz PH model with Gamma (shared) frailty for the frailty modelling of the MDR-TB mortality and its associated risk factors.
RESULTS: There were more MDR-TB deaths among females, HIV positive patients with pulmonary TB in the Khomas region. MDR-TB mortality was more likely to occur for patients who were aged 55 and above (HR = 3.57, $p < 0.001$, 95% CI: 2.18-5.91), HIV positive (HR = 2.07, $p < 0.001$, 95% CI: 1.39-3.08), and from the Khomas (HR = 3.68, $p = 0.001$, 95% CI: 1.72-7.87), Kunene (HR = 4.45, $p = 0.022$, 95% CI: 1.24-15.91), Omusati (HR = 2.70, $p = 0.022$, 95% CI: 1.15-6.31), and Oshana (HR = 2.51, $p = 0.021$, 95% CI: 1.15-5.48) regions.
CONCLUSIONS: It is therefore recommended that the Namibian government and policy

makers consider conducting outreach sessions to increase awareness on MDR-TB including early detection and screening programmes, and patient's adherence, especially among female patients aged 55 and above, with HIV and those living in these highlighted regions.

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11. Rifampicin-resistant Mycobacterium tuberculosis and unsuccessful results from Xpert® MTB/Rif-Ultra assay in Amhara Region, Ethiopia.

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BACKGROUND: Tuberculosis, an infectious disease caused by Mycobacterium tuberculosis (Mtb), causes 10 million new infections and 1.3 million deaths annually. The treatment of TB is hampered by the increasing incidence rate of drug resistance associated with TB. To diagnose TB and identify drug-resistant TB cases, rapid molecular technologies such as Xpert MTB/RIF, Truenat MTB, MTB Plus, and MTB-RIF Dx tests are recommended by the World Health Organization (WHO) and rolled out globally. Xpert MTB/RIF-Ultra assay is the

most widely used in developing countries like Ethiopia. However, this rapid technology has inherent limitations, such as error reports, invalid results, and no results collectively reported as unsuccessful tuberculosis results. The purpose of this study was to retrospectively evaluate the trend of rifampicin resistance and unsuccessful results in the Xpert MTB/RIF-Ultra assay facility of Northwest Ethiopia.
METHODS: Retrospective data archived in the Amhara Public Health Institute (APHI) TB laboratory from 2019 to 2024 were reviewed. Xpert MTB/RIF-Ultra software data were retrieved and transferred to Microsoft Excel. Then, it was checked for completeness, cleaned manually, and imported to Statistical Package for the Social Sciences (SPSS) version 25 software. The rate of mycobacterium tuberculosis (Mtb.) positives, multi-drug resistance tuberculosis (MDR-TB), and Unsuccessful results were analyzed from the total and year-wise. The final results were depicted using tables and different charts.
RESULTS: From June 30, 2019, to June 30, 2024, a total of 587,128 sputum samples were obtained from presumptive TB patients in 111 GeneXpert sites in the Amhara Region. Of these samples analyzed using Xpert MTB/RIF-Ultra, 6.17 % (36,212/587,128) were Mtb positive. Furthermore, the overall proportion of rifampicin resistance (RR) among Mtb-confirmed cases decreased to 3.03 % (1,096/36,212) and showed a downward trend from 4.62 % (184/3979) in 2020 to 2 % (176/8806) in 2024. The overall unsuccessful results (error, invalid & no result) were 6.48 %. The rate of unsuccessful results remained above the national target of < 5 % throughout the study periods.
CONCLUSION AND RECOMMENDATION: The rate of Mtb and MDR-TB showed a decreasing trend in the last six years in Northwest Ethiopia. However, unsuccessful results remained above the national target. The cause of unsuccessful results should be investigated, and the Xpert MTB/RIF-Ultra-related quality assurance system must be enhanced to reduce the rate of Xpert MTB/RIF-Ultra unsuccessful results.

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

12.Prevention and control of multidrug-resistance tuberculosis in Ethiopia: Patients' perspectives from the Oromia region.

PLoS One. 2025 May 12;20(5):e0322054. doi: 10.1371/journal.pone.0322054.

eCollection 2025.

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BACKGROUND: Multi-drug-resistant tuberculosis (MDR-TB) is one of the biggest challenges worldwide to end tuberculosis. It is vital to understand the challenges and opportunities of patients during MDR-TB treatment to enhance prevention and control efforts. The gap in research on the challenges and opportunities of patients during the screening, diagnosis, referral, and follow-up of MDR-TB prompted this study.
PURPOSE: The purpose of the study was to assess the challenges and opportunities for patients with MDR-TB during the diagnosis and treatment of MDR-TB in the Oromia region of Ethiopia.
METHODS: A qualitative approach was applied. The data were collected from 30 MDR-TB patients from 1 to 30 April 2022 using semi-structured interviews after written informed consent was signed by each participant to understand the challenges and opportunities of MDR-TB treatment. Data was analysed by thematic analysis using ATLAS.ti software.
RESULT: This article identifies challenges that include delays in diagnosis and treatment initiation due to inadequate diagnostic services, physical inaccessibility, and financial problems faced by patients to pay for transport, food, diagnosis, and accommodation. Other challenges included lack of psychosocial support, shortage of healthcare providers, poor communication, drug side effects, and interruption of food and housing support. In addition, participants mentioned opportunities, which include the availability of free diagnosis, treatment, and admission; availability of transport; food and housing allowance; and use of an ambulance for referral.
CONCLUSION: This study filled a research gap in Ethiopia by identifying challenges and opportunities during the MDR-TB treatment program. The MDR-TB treatment program should focus on improving inadequate screening and resources, shortage of healthcare providers, delays in the referral process, and non-compliance of patients.

DOI: 10.1371/journal.pone.0322054

PMCID: PMC12068706
PMID: 40354441 [Indexed for MEDLINE]

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

13.Long term outcomes in drug resistant tuberculosis with Bedaquiline, Pretomanid and varying doses of Linezolid.

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OBJECTIVES: Assess the effectiveness of bedaquiline, pretomanid and linezolid (BPaL) regimens with varying doses and duration of linezolid at the end of 48 weeks post treatment among drug resistant tuberculosis (DR TB) patients.
METHODS: Multicentric pragmatic randomized clinical trial in which BPaL regimens were given for 26 weeks for pulmonary pre extensively drug resistant tuberculosis (PreXDR TB); bedaquiline, pretomanid and linezolid 600mg for 26 weeks (arm1), structured dose reduction arms with linezolid dose reduction from 600 to 300mg after nine weeks (arm2) and 13 weeks (arm3). Participants were followed up for recurrence free cure up to 48 weeks post treatment. Whole genome sequencing in sputum samples at baseline and recurrence differentiated relapse and reinfection.
RESULTS: Of 403 enrolled, 378 were included for the modified intent to treat analysis based on baseline sputum culture positivity and sensitivity to medications in the study regimen. Among them, 331(88%) had recurrence free cure at the end of 48 weeks of post treatment follow-up; arm1:112(87%), arm2:110(88%), arm3:109(88%). Overall, 14 (12 bacteriological and 2 clinical) recurrences (arm1-four, 2-six and 3-four) occurred; 11 recurrences occurred within 24 weeks after treatment completion; four out of 11 within the first 12 weeks. Of the 10 paired sputum samples available at baseline and recurrence for comparison of lineages, there were two reinfections and eight relapses.
CONCLUSION: Structured dose reduction arms had comparable recurrence free cure rates as linezolid 600mg arm when given along with bedaquiline and pretomanid for 26 weeks in PreXDR TB. Most of the recurrences occurred within the first six months.

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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.

14. **Supporting multidrug-resistant or rifampicin-resistant TB treatment adherence in people with harmful use of alcohol through person-centred care.**

Int Health. 2025 May 1;17(3):313-323. doi: 10.1093/inthealth/ihae066.

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BACKGROUND: TB is concentrated in populations with complex health and social issues, including alcohol use disorders (AUD). We describe treatment adherence and outcomes in a person-centred, multidisciplinary, psychosocial support and harm reduction intervention for people with multidrug-resistant or rifampicin-resistant TB (MDR/RR-TB) with harmful alcohol use.
METHODS: An observational cohort study, including multilevel mixed-effects logistic regression and survival analysis with people living in Minsk admitted with MDR/RR-TB and AUD during January 2019-November 2021 who received this person-centred, multidisciplinary, psychosocial support and harm reduction intervention, was conducted.
RESULTS: There were 89 participants enrolled in the intervention, with a median follow-up of 12.2 (IQR: 8.1-20.5) mo. The majority (n=80; 89.9%) of participants had AUD, 11 (12.4%) also had a dependence on other substances, six (6.7%) a dependence on opioids and three (3.4%) a personality disorder. Fifty-eight had a history of past incarceration (65.2%), homelessness (n=9; 10.1%) or unemployment (n=55; 61.8%). Median adherence was 95.4% (IQR: 90.4-99.6%) and outpatient adherence was 91.2% (IQR: 65.1-97.0%). Lower adherence was associated with hepatitis C, alcohol plus other substance use and outpatient facility-based treatment, rather than video-observed treatment, home-based or inpatient treatment support.
CONCLUSIONS: This intervention led to good adherence to MDR/RR-TB treatment in people with harmful use of alcohol, a group usually at risk of poor outcomes.

Poor outcomes were associated with hepatitis C, other substance misuse and outpatient facility-based treatment support.

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PMID: 39501994 [Indexed for MEDLINE]

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

15.**Drug-resistant tuberculosis profiles among patients presenting at the antituberculosis center of Brazzaville, Republic of Congo.**

Ann Clin Microbiol Antimicrob. 2025 May 9;24(1):31. doi: 10.1186/s12941-025-00786-8.

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BACKGROUND: WHO strategy to end Tuberculosis (TB) calls for drug susceptibility testing of Mycobacterium tuberculosis (MTB) for all patients, in high TB burden settings. Thus, this study aimed to investigate the MTB drug resistance profiles and related risk factors among patients presenting to the Antituberculosis Center of Brazzaville, Republic of Congo.
METHODS: A cross-sectional study was carried out from July 2022 to August 2023 involving 1,121 presumptive pulmonary tuberculosis patients enrolled to the Antituberculosis Center of Brazzaville. Sputum samples were collected from all the study participants for the diagnosis of tuberculosis and rifampicin resistance, using the Xpert MTB/RIF (Cepheid, USA) assay. Samples positive for MTB with drug resistance to RIF were further tested for the second line anti-MTB drug susceptibility using the 10-color Xpert MTB/XDR assay.
RESULT: Out of 1,121 presumptive TB patients tested, 302/1,121 (26.9%) were MTB positive. Among these, 18/302 (6.0%) had received previous TB treatment and 15/302 (5.0%) were HIV co-infected. The mean age of the study population was 34 years, with a higher prevalence in males (69.2%). Of the MTB isolates, 25/302 (8.3%) were Rifampicin-resistant, with 24/25 (96%) further confirmed as multi-resistant strains, including 6/24 (25%) pre-XDR. Risk factors for MDR-TB included a history of TB treatment (AOR = 8.96, p = 0.002) and chronic cough (AOR = 7.14, p = 0.003).
CONCLUSIONS: This study reveals a high level of drug-resistant tuberculosis in Brazzaville, with previous TB treatment being a significant risk factor. The findings underscore the need to strengthen molecular surveillance and TB management and control measures in the Republic of Congo.

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PMCID: PMC12065265
PMID: 40346665 [Indexed for MEDLINE]

Conflict of interest statement: Declarations. Ethical approval: An ethical clearance was obtained from the ethics committee of the Fondation Congolaise pour la Recherche Médicale after the review of the protocol. Prior to enrolment, participants were informed about the purpose of the study and written informed consent was obtained from each recruited participant. For participants between 8

and 17 years old, assent was obtained from the individuals and signed informed consent was obtained from parents or guardians. Potential conflicts of interest: The authors declare no competing interests.

16.**Verapamil and its metabolite norverapamil inhibit the Mycobacterium tuberculosis MmpS5L5 efflux pump to increase bedaquiline activity.**

Proc Natl Acad Sci U S A. 2025 Apr 22;122(16):e2426827122. doi: 10.1073/pnas.2426827122. Epub 2025 Apr 17.

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Bedaquiline is the cornerstone of a new regimen for the treatment of drug-resistant tuberculosis. However, its clinical use is threatened by the emergence of bedaquiline-resistant strains of Mycobacterium tuberculosis. Bedaquiline targets mycobacterial ATP synthase but the predominant route to clinical bedaquiline resistance is via upregulation of the MmpS5L5 efflux pump due to mutations that inactivate the transcriptional repressor Rv0678. Here, we show that the MmpS5L5 efflux pump reduces susceptibility to bedaquiline as well as its new, more potent derivative TBAJ-876 and other antimicrobial substrates, including clofazimine and the DprE1 inhibitors PBTZ-169 and OPC-167832. Furthermore, the increased resistance of Rv0678 mutants stems entirely from increased MmpS5L5 expression. These results highlight the potential of a pharmacological MmpS5L5 inhibitor to increase drug efficacy. Verapamil, primarily used as a calcium channel inhibitor, is known to inhibit diverse efflux pumps and to potentiate bedaquiline and clofazimine activity in M. tuberculosis. Here, we show that verapamil potentiates the activity of multiple diverse MmpS5L5 substrates. Using biochemical approaches, we demonstrate that verapamil does not exert this effect by acting as a disruptor of the protonmotive force used to power MmpS5L5, as previously proposed, suggesting that verapamil inhibits the function of the MmpS5L5 pump. Finally, norverapamil,

the major verapamil metabolite, which has greatly reduced calcium channel activity, has equal potency in reducing resistance to MmpS5L5 substrates. Our findings highlight verapamil's potential for enhancing bedaquiline TB treatment, for preventing acquired resistance to bedaquiline and other MmpS5L5 substrates, while also providing the impetus to identify additional MmpS5L5 inhibitors.

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

17. Diagnosis, management, and outcomes of drug-induced erythrocytosis: a systematic review.

Blood Adv. 2025 May 13;9(9):2108-2118. doi: 10.1182/bloodadvances.2024015410.

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Secondary erythrocytosis refers to an elevation in hemoglobin or hematocrit due to elevated serum erythropoietin levels. Medications including testosterone and sodium-glucose cotransporter-2 (SGLT-2) inhibitors are increasingly recognized as causes of secondary erythrocytosis. We conducted a systematic review to inform the clinical management of drug-induced erythrocytosis. Following Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, we performed a systematic literature search in MEDLINE, EMBASE, CENTRAL (all via Ovid), and Google Scholar. Of the 2036 articles screened for eligibility, 45 studies were included in our review, with 35 studies on testosterone and other androgen use, 5 studies on SGLT-2 inhibitors, 3 studies on antiangiogenic tyrosine kinase inhibitors (TKIs), 1 study on erythropoiesis-stimulating agents, and 1 study on a treatment regimen for multidrug-resistant tuberculosis.

Cisgender and transgender men on prescription testosterone had erythrocytosis rates of up to 66.7%, with intramuscular formulations, higher doses, and older age associated with increased risk of erythrocytosis. Up to 2.7% of men on testosterone therapy developed thromboembolic events. Among individuals on SGLT-2 inhibitors, erythrocytosis rates ranged from 2.1% to 22%, with those who discontinued therapy demonstrating improvement or resolution of erythrocytosis. Thromboembolic events were reported in up to 10% of these individuals. Antiangiogenic TKIs were studied in patients with cancer, with erythrocytosis developing in up to 43.5% of patients. Drug-induced erythrocytosis is a heterogeneous condition for which there is no clear consensus among clinicians about its diagnosis and management. We offer recommendations for clinical practice within the scope of this systematic review, although further research is required.

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PMID: 39913688 [Indexed for MEDLINE]

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18.Tuberculosis mortality and drug resistance among patients under TB treatment before and during COVID-19 in Burundi: a case-control study.

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BACKGROUND: The coronavirus SARS-CoV-2 (COVID-19) experience has underscored the consequences of inequalities in health and access to health services across and within countries. Vulnerable population groups have been disproportionately exposed to certain diseases such as tuberculosis (TB) due to service interruptions. The current study aimed to assess TB related mortality and risk of drug resistance during the COVID-19 Pandemic in Burundi.
METHODS: We conducted an incident case-control study on 362 TB patients, with 181 multidrug resistant TB (MDR-TB) patients and 181 drug susceptible TB (DS-TB) patients. These patients under TB treatment between July 11, 2018, and November 11,2022 (18 months before and 18 months during COVID-19). Baseline and drug susceptibility status data were captured at treatment initiation. Mortality during treatment follow-up TB mortality was compared between categories of drug susceptibility, period (before vs during COVID-19) and regimen phase. A multivariate logistic regression was used to show the predictive risk factors. K-Fold cross-validation was used to evaluate the final model.
RESULTS: A half of TB patients was under 40 years old, with majority of them being unemployed, malnourished and lacking food support during TB treatment. Most of them lived in precarious conditions with limited access to healthcare services. The overall TB-related mortality was 16.0% (95% CI: 12.5%- 20.3%) with 15.5% (95%CI: 10.7%-21.8%) in MDR-TB patients and 16.6% (95% CI: 11.6%-22.9%) in DS-TB patients. Stratified by the period, TB related mortality was 15.3% (95%CI: 11.7%-20.9%) before the COVID-19 pandemic and 17.1% (95%C 11.5%-24.6%) during the COVID-19 pandemic. More than a half of deaths in TB patients occurred during intensive phase of treatment. The risk of MDR-TB was significantly higher ($p < 0.05$) among patients undergoing treatment during the pandemic, those with a low education level, living in rural areas, unemployed, using public transportation, or living in overcrowded households (big family size,a small number of rooms). Additionally, patients with history of TB, previous treatment failure, and close contact with MDR-TB patients were more likely to have MDR-TB. The likelihood of MDR-TB further increased with the cumulative presence of these risk factors on the same TB patient.
CONCLUSION: TB mortality increased during the COVID-19 pandemic, particularly among MDR-TB patients. The odds of MDR-TB encompass a range of socio demographic and clinical factors particularly among economically disadvantaged patients. These findings underscore the need for targeted equity-driven interventions in high-risked populations, especially in the context of emerging outbreaks, in order accelerate TB elimination goals. Additional investigation on TB related mortality should focus on the intensive phase of treatment, which aligns with the 2025 World Health Organization consolidated guidelines on TB diagnosis and control.

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PMCID: PMC12085829
PMID: 40382541 [Indexed for MEDLINE]

Conflict of interest statement: Declarations. Ethics approval and consent to participate: The study was approved by an institutional ethics committee of Kamenge Teaching Hospital (N/Ref.2022/DGCHUK836/11.5). The study met the criteria for exemption from the regulations found at 45 CFR46.104(d) (4). No informed consent was needed. The Harvard T.H. Chan School of Public Health IRB office (RB23-1209) has, additionally, waived the requirement for informed consent. All data were fully anonymized before we accessed them. The study was conducted by the guidelines of the Declaration of Helsinki. Consent for publication: Not applicable. Competing interests: The authors declare no competing interests.

19.Effectiveness of a bedaquiline, linezolid, clofazimine 'core' for multidrug-resistant TB.

IJTLD Open. 2025 May 12;2(5):269-275. doi: 10.5588/ijtldopen.24.0515. eCollection 2025 May.

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Update of
medRxiv. 2024 Jan 19:2024.01.18.24301453. doi: 10.1101/2024.01.18.24301453.

BACKGROUND: Treatment outcomes may be compromised among individuals with multidrug/rifampicin-resistant TB (MDR/RR-TB) with fluoroquinolone (FQ) resistance. Among people in whom an FQ was unlikely to be effective, we compared the effectiveness of longer individualised regimens comprised of bedaquiline (Bdq) for 5-8 months, linezolid, and clofazimine to those reinforced with at least 1 Group C drug and/or longer Bdq duration.
METHODS: We emulated a target trial to compare the effectiveness of initiating and remaining on the core regimen to a regimen reinforced with 1) Bdq for ≥9 months, 2) Bdq for ≥9 months, and delamanid (Dlm), 3) imipenem (Imp), 4) a second-line injectable, or 5) Bdq for ≥9 months, Dlm and Imp. We used cloning, censoring, and inverse-probability weighting to estimate the probabilities of successful treatment.
RESULTS: Adjusted probabilities of successful treatment ranged from 0.75 (95% CI 0.61-0.89) to 0.84 (95% CI 0.76-0.91). Ratios of treatment success ranged from 1.01 for regimens reinforced with Bdq ≥9 months (95% CI 0.79-1.28) and Bdq ≥9 months plus Dlm (95% CI 0.81-1.31) to 1.11 for regimens reinforced with an injectable (95% CI 0.92-1.39) and Bdq ≥9 months, Dlm and Imp (95% CI 0.90-1.41).
CONCLUSIONS: Some reinforced regimens had modestly higher treatment success rates, but estimates were imprecise. Additional studies of strategies for maximising treatment success among individuals with FQ resistance are needed.

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PMCID: PMC12068452
PMID: 40365032

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20. Phenotypic and genotypic resistance to bedaquiline in patients with multi-drug-resistant tuberculosis-experiences from Armenia.

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Risk factors for baseline bedaquiline (BDQ) resistance, amplification during treatment, and correlations with treatment outcomes are not fully understood. This cohort included Armenian patients with multidrug-resistant TB predominantly fluoroquinolone-resistant enrolled between 2013 and 2015 in a BDQ compassionate use program. BDQ resistance at baseline and during treatment was assessed using MGIT (pDSTMGIT), minimal inhibitory concentration in 7H11 (MIC7H11), and whole-genome sequencing. Risk factors, such as treatment effectiveness or stage of the disease, were analyzed for association with baseline BDQ resistance, acquired BDQ resistance, and treatment outcome. Among 39 patients, baseline BDQ resistance was 6% (2/33) by pDSTMGIT and 7% (2/29) by MIC7H11. All four baseline isolates with an Rv0678 mutation were phenotypically resistant. During

treatment, 48% of the patients acquired BDQ resistance by pDSTMGIT, and 52% acquired mutations at various frequencies (97% in Rv0678). None of the factors significantly contributed to baseline or acquired BDQ resistance. Unfavorable treatment outcome (41%) was more frequent in the presence of acquired Rv0678 mutations [odds ratio (OR) 132, 95% confidence interval (CI) 7.43, 2375], phenotypic BDQ resistance (OR 176, 95% CI 6.48, 2423), or MIC increase above or below the critical concentration (both OR 84.3, 95% CI 2.93, 2423) during treatment. For these highly treatment-experienced patients, low baseline prevalence but high incidence of acquired BDQ resistance was observed. Acquisition of mutations in BDQ candidate resistance genes, regardless of their frequency, or increased MICs during treatment, even below the critical concentration, should be seen as a warning sign of resistance amplification and increased risk of unfavorable treatment outcome.

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

Int Health. 2025 May 1;17(3):292-303. doi: 10.1093/inthealth/ihae059.

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BACKGROUND: Evidence of time to culture conversion is used to predict the time of cure from the disease and the overall drug-resistant tuberculosis (TB) treatment duration. Even though evidence about sputum culture conversion is enormous in TB treatment, no study has yet been done in our areas, where cases are common. The study aimed to assess the time to sputum conversion and its predictors among drug-resistant TB patients from October 2013 to September 2021

in eastern Ethiopia.
METHODOLOGY: A retrospective cohort study was conducted in eastern Ethiopia among 273 drug-resistant TB patients who were treated from October 2013 to September 2021 at Dire Dawa City and Harari regional treatment centres. The Kaplan-Meier method was used to estimate the median time of sputum culture conversion. Cox proportional hazards regression was employed to detect the predictors of sputum culture conversion. An adjusted hazard ratio (aHR) with 95% confidence interval (CI) was used to determine the strength and significance of the association.
RESULTS: Of the 273 drug-resistant TB patients, the sputum culture of 216 (79.12%) patients became negative in a median time of 3 months (interquartile range 2-7). The time to sputum culture conversion was negatively associated with underweight (aHR 0.65 [95% CI 0.49 to 0.90]) and poor adherence (aHR 0.41 [95% CI 0.24 to 0.69]). The time to sputum culture conversion was also positively associated with patients resistant to two or more drugs (aHR 1.58 [95% CI 1.07 to 2.32]) and patients receiving a short treatment regimen (aHR 2.24 [95% CI 1.10 to 2.55]).
CONCLUSIONS: A shorter culture conversion rate was observed compared with the median time recommended by the World Health Organization. Being underweight, poor adherence to treatment, resistance to two or more drugs and receiving a short treatment regimen were found to be predictors of time to sputum culture conversion. Implementing nutrition assessment, counselling and support of drug adherence may improve sputum culture conversion.

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Conflict of interest statement: None declared.

22. Genetic insights in infectious diseases: Insights from a case report and implications for personalized medicine.

World J Clin Cases. 2025 May 6;13(13):101438. doi: 10.12998/wjcc.v13.i13.101438.

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The relationship between genetics and infectious diseases is important in shaping our understanding of disease susceptibility, progression, and treatment. Recent research shows the impact of genetic variations, such as heme-oxygenase promoter length, on diseases like malaria and sepsis, revealing both protective and inconclusive effects. Studies on vaccine responses highlight genetic markers like human leukocyte antigens, emphasizing the potential for personalized immunization strategies. The ongoing battle against drug-resistant tuberculosis (TB) illustrates the complexity of genomic variants in predicting resistance, highlighting the need for integrated diagnostic tools. Additionally, genome-wide association studies reveal antibiotic resistance mechanisms in bacterial genomes, while host genetic polymorphisms, such as those in solute carrier family 11 member 1 and vitamin D receptor, demonstrate their role in TB susceptibility. Advanced techniques like metagenomic next-generation sequencing promise detailed pathogen detection but face challenges in cost and accessibility. A case report involving a highly virulent Mycobacterium TB strain with the pks1 gene further highlights the need for genetic insights in understanding disease severity and developing targeted interventions. This evolving landscape emphasizes the role of genetics in infectious diseases, while also addressing the need for standardized studies and accessible technologies.

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PMID: 40330288

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23. Early treatment monitoring of multidrug-resistant tuberculosis based on CT radiomics of cavity and cavity periphery.

Eur Radiol Exp. 2025 Apr 26;9(1):43. doi: 10.1186/s41747-025-00581-2.

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BACKGROUND: Early identification of treatment failure can effectively improve the success rate of antituberculosis treatment. This study aimed to construct a predictive model using radiomics based on cavity and cavity periphery to monitor the early treatment efficacy in multidrug-resistant tuberculosis (MDR-TB).
METHODS: We retrospectively collected data on 350 MDR-TB patients who underwent pretreatment chest computed tomography (CT) and received longer regimens from two hospitals. They were subdivided into training (252 patients from hospital 1) and testing (98 patients from hospital 2) cohorts. According to at least two consecutive sputum culture results within the early sixth months of treatment, patients were divided into high-risk and low-risk groups. Radiomics models were established based on cavity and periphery with a range of 2, 4, 6, 8, and 10 mm. A combined model fused radiomics features of cavity with the best-performing peripheral regions. The performance of these models was evaluated by the receiver operating characteristic area under the curve (AUC) and clinical decision curve analysis.
RESULTS: The cavity model achieved AUCs of 0.858 and 0.809 in the training and testing cohort, respectively. The radiomics model based on 4 mm peripheral region showed superior performance compared to other surrounding areas with AUCs of 0.884 and 0.869 in the two cohorts. The AUCs of the combined model were 0.936 and 0.885 in the two cohorts.
CONCLUSION: CT radiomics analysis integrating cavity and cavity periphery provided value in identifying MDR-TB patients at high risk of treatment failure. The optimal periphery extent was 4 mm.
RELEVANCE STATEMENT: The cavity periphery also contains therapy-related information. Radiomics model based on cavity and 4 mm periphery is an effective adjunct to monitor early treatment efficacy for MDR-TB patients that can guide clinical decision.
KEY POINTS: A combined CT radiomics model integrating cavity with periphery can effectively monitor treatment response. A periphery of 4 mm showed superior performance compared to other peripheral smaller or greater extent. This study provided a surrogate for identifying the high risk of treatment failure in multidrug-resistant tuberculosis patients.

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PMCID: PMC12033146
PMID: 40285894 [Indexed for MEDLINE]

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24. Experiences of children and their caregivers affected by multidrug-resistant tuberculosis in Cape Town, South Africa.

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BACKGROUND: Approximately 30,000 children (<15 years) develop multidrug-resistant (MDR) tuberculosis (TB) each year. MDR-TB severely impacts the lives of children and their families, yet data exploring their experiences are limited. We describe the experiences of children routinely treated for MDR-TB and their caregivers throughout their MDR-TB journeys in Cape Town, South Africa.
METHODS: We conducted a series of three in-depth qualitative interviews (48 interviews in total) with 17 children (<15 years) and/or their caregivers between April 2021 and September 2021. We selected children who had been routinely treated for MDR-TB between 2018 and 2021. We applied a deductive, thematic analysis to case summaries with illustrative examples from interviews.

FINDINGS: Children had negative experiences throughout their MDR-TB journey, before their diagnosis, during the diagnostic process, through treatment, and beyond treatment completion. Children and their caregivers experienced delays in acquiring accurate and timely MDR-TB diagnosis; stating lack of symptom recognition and repeated referrals between health facilities. Once on treatment, caregivers experienced challenges administering MDR-TB medication as children resisted taking their medications due to poor palatability, tolerability, and negative side effects. Some caregivers reported that, beyond treatment, children experienced extended physical challenges such as shortness of breath. Additionally, MDR-TB diagnosis and treatment negatively affected family life, as caregivers adjusted household spending toward foods that facilitated ingestion and mitigated side effects. Caregivers also juggled between attending to their children's MDR-TB care and other household priorities.
CONCLUSION: There are multifactorial challenges experienced by children and their caregivers throughout their MDR-TB journey. Research is needed to develop holistic interventions for child-caregiver-centred psychosocial support to mitigate the negative impact of MDR-TB on children and their caregivers through prevention, earlier diagnosis, and simpler, child-friendly regimens. [1112,3].

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PMID: 40388384 [Indexed for MEDLINE]

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

25. Treatment outcomes and predictors of success for multidrug resistant tuberculosis MDR TB in Ugandan regional referral hospitals.

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Multidrug-resistant tuberculosis (MDR-TB) is a form of tuberculosis caused by strains resistant to both isoniazid and rifampicin, the most critical first-line drugs. Managing MDR-TB presents substantial challenges due to prolonged and costly treatment regimens, which are less effective than those for drug-susceptible TB. These difficulties are further exacerbated in low-resource settings by inadequate healthcare infrastructure, limited diagnostic capacity, and suboptimal access to treatment. Uganda, a high-burden TB country, faces persistent challenges in meeting national MDR-TB treatment targets, with high mortality rates and unfavourable outcomes. This study evaluated the treatment outcomes and factors associated with success among MDR-TB patients in regional referral hospitals. Of the 293 registered patients, 284 were included in the analysis, with a median age of 38 years (IQR: 30-45) and a predominance of male patients (65.1%). Overall, 68.7% of patients achieved successful treatment outcomes, while 31.3% experienced unfavourable outcomes. Multivariate analysis identified weight at treatment initiation (41-49 kg) as significantly associated with poor outcomes. These findings highlight a treatment success rate below national targets, with persistent high mortality and treatment failure in several regions. Addressing these challenges requires the development of innovative therapies and personalized care strategies to improve MDR-TB management in Uganda.

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Conflict of interest statement: Declarations. Competing interests: The authors declare no competing interests. Ethics approval and consent to participate: We obtained ethical approval and a waiver of informed consent from the Research and Ethics Committee of Mbale Regional Referral Hospital, approval number MRRH-2021-70. This was accompanied by administrative clearance from Mbale, Soroti, Moroto, and Lira Regional Referral Hospitals. All study procedures were done in accordance with the ethical guidelines of the 1975 Declaration of Helsinki. Confidentiality and anonymity of the participants' information were strictly maintained throughout the study. Data were de-identified to protect personal information, and access to the data was restricted to the research team.

26. Sanfetrinem, an oral β-lactam antibiotic repurposed for the treatment of tuberculosis.

Drug Resist Updat. 2025 May;80:101213. doi: 10.1016/j.drup.2025.101213. Epub 2025 Feb 15.

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Update of
bioRxiv. 2024 Oct 10:2024.10.10.617558. doi: 10.1101/2024.10.10.617558.

Tuberculosis (TB) is historically the world's deadliest infectious disease. New TB drugs that can avoid pre-existing resistance are desperately needed. The β-lactams are the oldest and most widely used class of antibiotics to treat bacterial infections but, for a variety of reasons, they were largely ignored until recently as a potential treatment option for TB. Recently, a growing body of evidence indicates that later-generation carbapenems in the presence of β-lactamase inhibitors could play a role in TB treatment. However, most of these drugs can only be administered intravenously in the clinic. We performed a screening of β-lactams against intracellular Mycobacterium tuberculosis (Mtb) and identified sanfetrinem cilexetil as a promising oral β-lactam candidate. Preclinical in vitro and in vivo studies demonstrated that: (i) media composition impacts the activity of sanfetrinem against Mtb, being more potent in the presence of physiologically relevant cholesterol as the only carbon source, compared to the standard broth media; (ii) sanfetrinem shows broad spectrum activity against Mtb clinical isolates, including MDR/XDR strains;

(iii) sanfetrinem is rapidly bactericidal in vitro against Mtb despite being poorly stable in the assay media; (iv) there are strong in vitro synergistic interactions with amoxicillin, ethambutol, rifampicin and rifapentine and, (v) sanfetrinem cilexetil is active in an in vivo model of infection. These data, together with robust pre-clinical and clinical studies of broad-spectrum carbapenem antibiotics carried out in the 1990s by GSK, identified sanfetrinem as having potential for treating TB and catalyzed a repurposing proof-of-concept Phase 2a clinical study (NCT05388448) in South Africa.

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PMCID: PMC11960770
PMID: 40020440 [Indexed for MEDLINE]

Conflict of interest statement: Declaration of Competing Interest RGdR, MPAC, JR, SA, MCI, EPdF, EPH, ASV, AML, SFB, DBA and RHB are or were employees of GSK, a producer of the generic drug amoxicillin/clavulanate and sanfetrinem. SRG, RGdR, AML, DBA and RHB are inventors of the patent describing the antituberculosis activity of sanfetrinem (WO2018206466A1). CJT declare no conflicts of interest. All authors approved the submission of the document.

27. Provision of care for people with HIV migrating from Ukraine: preparing for a long-term response.

AIDS. 2025 May 1;39(6):629-638. doi: 10.1097/QAD.0000000000004147. Epub 2025 Apr 3.

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Russia's invasion and war in Ukraine have caused a major humanitarian crisis among Ukrainian citizens, but also specifically affected diagnosis and provision of HIV care. As Ukraine remains the country with the second highest (after Russia) HIV incidence in Europe, the forced migration resulting from the war has required urgent and targeted responses to allow for uninterrupted access to medical care and antiretroviral drug supply in neighboring countries and beyond. Response and integration of people with HIV (PWH) has been swift across European countries, but several challenges remain. Key challenges relate to the expansion of unstigmatized HIV testing to tackle late diagnoses, development of legal frameworks allowing for access to medication not registered or under patent protection in other European countries, diagnosis and treatment of key comorbidities including tuberculosis (TB) and hepatitis C virus (HCV), vaccination programs, and continued surveillance for drug resistance and changes in molecular epidemiology.

DOI: 10.1097/QAD.0000000000004147
PMCID: PMC11970604
PMID: 40176534 [Indexed for MEDLINE]

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28. Utility of Rapid Molecular Assays for Detecting Multidrug-Resistant Mycobacterium tuberculosis in Extrapulmonary Samples.

Diagnostics (Basel). 2025 Apr 28;15(9):1113. doi: 10.3390/diagnostics15091113.

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Background: Extrapulmonary tuberculosis (TB) presents significant diagnostic challenges, particularly in the context of multidrug-resistant (MDR) strains. This study assessed the utility of the WHO-recommended rapid molecular assays, originally validated for pulmonary TB, in diagnosing extrapulmonary TB and detecting the MDR Mycobacterium tuberculosis complex (MTBC). Materials and Methods: A total of 6274 clinical samples, including 4891 pulmonary and 1383 extrapulmonary samples, were analyzed between 2019 and 2022 using the BD MAX™ MDR-TB assay (BD MAX), the Xpert® MTB/RIF assay (Xpert MTB/RIF), the Xpert® MTB/XDR assay (Xpert MTB/XDR), FluoroType MTB, and phenotypic drug susceptibility testing (DST). Results: MTBC was detected in 426 samples using BD MAX (376 pulmonary and 50 extrapulmonary), of which 277 were culture-confirmed. Phenotypic testing confirmed 299 positive cultures on Löwenstein-Jensen (LJ) medium and 347 in BD BACTEC™ MGIT™ (BACTEC MGIT) mycobacterial growth indicator tube (BBL) liquid culture. BD MAX showed high sensitivity and specificity for extrapulmonary TB detection (93.1% and 98.4%, respectively). Resistance to isoniazid or rifampicin was identified in 11% of MTBC-positive cases, whereas 3.69% were confirmed as MDR-TB. The molecular assays effectively detected resistance-associated mutations (katG, inhA, and rpoB), with high concordance to phenotypic tests (DST) (κ = 0.69-0.89). Conclusions: This study demonstrates that molecular assays, although validated for pulmonary TB, are also reliable for extrapulmonary TB detection and drug resistance profiling. Their rapid turnaround and robust accuracy support broader implementation in routine diagnostics, especially for challenging extrapulmonary specimens where early detection is critical for targeted therapy.

DOI: 10.3390/diagnostics15091113
PMCID: PMC12071935
PMID: 40361931

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

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BACKGROUND: This study aimed to develop and validate a predictive model based on multimodal data, including clinical features, radiomics features, and deep learning features, to distinguish multidrug-resistant tuberculosis (MDR-TB) in HIV/AIDS patients, thereby improving diagnostic accuracy.
METHODS: A retrospective cohort of HIV/AIDS patients with drug-sensitive tuberculosis (n = 164) and MDR-TB (n = 63) admitted to the Fourth People's Hospital of Nanning between January 2016 and July 2024 was included. The dataset was randomly divided into training and validation sets at a 7:3 ratio. A multimodal model was constructed by integrating a clinical model, a radiomics model, and a 2.5D multi-instance learning (MIL) approach.
RESULTS: Key predictors-platelet count and C-reactive protein-were identified through univariate and multivariate logistic regression analysis. The integrated model achieved the highest performance in both the training and validation set (AUC=0.943 and 0.899, respectively), significantly outperforming individual models. Grad-CAM effectively localized key image regions influencing decision-making, while a nomogram quantified the contribution weights of each predictor, enhancing model transparency. The Hosmer-Lemeshow (HL) test confirmed good model calibration, and the decision curve analysis (DCA) curve demonstrated the optimal clinical net benefit of the integrated model.
CONCLUSION: The multimodal integrated model developed in this study significantly improved the diagnostic efficacy of MDR-TB in HIV/AIDS patients by combining clinical, radiomics, and deep learning features, providing a reliable tool for individualized precision diagnosis and treatment.

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relationships that could have appeared to influence the work reported in this paper.

30.Care-seeking and treatment pathways of multidrug-resistant tuberculosis patients: an analysis of real-world data from regional health information system in Ningbo City in Eastern China.

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OBJECTIVES: The patient pathway of multidrug-resistant tuberculosis (MDR-TB) in China is an essential but not well-studied area. This study aimed to understand the alignment between patient-initiated care-seeking demands for MDR-TB and the availability of diagnostic and treatment services in Ningbo, a city in eastern China, using patient pathway analysis (PPA).
METHODS: We collected the diagnostic and treatment data of 240 patients with MDR-TB in Ningbo from 2015 to 2019. Using patient pathway analysis, we matched the medical data of patients from different medical institutions and mapped their care pathways to illustrate their access to medical services.
RESULT: Our study indicated that the proportion of patients with MDR-TB who

chose non-TB-designated medical institutions (55%) was higher than those who chose TB-designated medical institutions (45%) at their initial visit. An estimated 69% of patients with MDR-TB patients received initial TB screening services during their first visit. In this study, 47% of patients needed to visit 4-7 medical institutions to be diagnosed with MDR-TB. Overall, 80% (n = 192) of patients were diagnosed with MDR-TB within four visits, while 13% (n = 30), 4% (n = 10), and 3% (n = 8) of patients were not diagnosed at the fourth visit and remained at level 2, 1, and 0 medical institutions, respectively.
CONCLUSION: The care-seeking pathway of patients with MDR-TB in Ningbo is complex. This indicates room for improvement in local diagnosis and referral services. There is a need to promote the deployment of MDR-TB screening, diagnosis, and treatment services at lower-level institutions.

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31. Spatial analysis of drug resistant tuberculosis (DRTB) incidence and relationships with determinants in Rio de Janeiro state, 2010 to 2022.

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BACKGROUND: The aim of this study was to assess the spatial distribution of

drug-resistant tuberculosis (DRTB) cases in Rio de Janeiro state and its association with demographics, socioeconomic and health determinants.
METHODS: An ecological study based on real-world DRTB data from 2010 to 2022, in the Rio de Janeiro state, using data from the Special Tuberculosis Treatment Information System (SITE-TB) and demographic census. Crude incidence rates (CIR) of DRTB per 100,000 inhabitants and smoothed rates through the Global and Local Empirical Bayesian (BEG and BEL) methods were calculated. Spatial autocorrelation was explored using Moran's I statistic, Local Indicators of Spatial Association (LISA), and the Getis-Ord statistics. The SCAN method was also used to identify spatial-time clusters. To analyze the association of DRTB and determinants, we used LISA bivariate for spatial correlation and four explanatory statistical models were listed.
RESULTS: From 2010 to 2022, 2,709 new cases of DRTB were reported (CIR 16.9/100,000 inhabitants). The municipalities in the metropolitan region of Rio de Janeiro state had the highest rates. Despite 41% of municipalities reporting no new cases, BEG and BEL suggested higher rates than CIR, indicating underreporting. Spatial heterogeneity was observed, and spatial and spatial-temporal clusters and hotspots were detected in metropolitan region. Family health strategy coverage was identified as protection factor, however a not expected negative spatial autocorrelation between CIR and health strategy coverage, primary care and healthcare agent coverage was found. The variables identified as risk factors were population aged ≥18 years old with Elementary School completed (OR:1.10; CI95%:1.04-1.16), demographic density (OR: 1.00; CI95%:1.00-1.01), HIV-TB coinfection (OR: 1.18; CI95%:1.06-1.31).
CONCLUSION: The identification of areas of risk for DRTB, spatial correlation and association between incidence and determinants, demonstrates that the DRTB transmission dynamics is related to the perpetuation of social inequality and urban spatial organization.

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

32. Clinical Features of Anti-Tuberculosis Drug-Induced Liver Injury and Risk Factors for Severe Cases: A Retrospective Study in China.

Infect Drug Resist. 2025 Apr 25;18:2065-2078. doi: 10.2147/IDR.S519211.
eCollection 2025.

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BACKGROUND: Anti-tuberculosis drug-induced liver injury (ATB-DILI) is a common adverse reaction associated with tuberculosis (TB) treatment, significantly impacting treatment adherence and therapeutic outcomes. However, large-scale studies on hospitalized patients in China remain limited.
PURPOSE: To characterize the clinical features and liver injury patterns in hospitalized TB patients with ATB-DILI and to identify risk factors associated with severe ATB-DILI.
METHODS: We retrospectively reviewed 28,753 hospitalized TB patients at Beijing Chest Hospital from 2014 to 2023. ATB-DILI was diagnosed in 567 patients (2.0%) based on serum biochemical criteria and causality assessment. Demographic, clinical, and laboratory data were analyzed to characterize liver injury types and identify risk factors for severe cases. Subgroup analyses based on liver injury patterns were performed to further evaluate the association between age and severe ATB-DILI.
RESULTS: Overall, 567 cases with ATB-DILI (2.0%) were analyzed. Hepatocellular injury was the most common type (71.4%), followed by cholestatic (13.8%) and mixed (14.8%) injury patterns. Most patients (68.4%) were asymptomatic and diagnosed via routine biochemical monitoring; jaundice occurred in 18.2%. Patients with hepatocellular damage were significantly younger, while those with cholestatic injury were older ($p < 0.001$). Severe ATB-DILI occurred in 46 patients (8.1%), with advanced age (≥60 years) identified as an independent risk factor (OR = 2.45, 95% CI: 1.33-4.52, $p = 0.004$). Subgroup analysis showed that this association between age and severe ATB-DILI was significant in the hepatocellular injury type (unadjusted OR = 3.59, 95% CI: 1.61-8.02, $p = 0.002$), while no statistically significant association was observed in cholestatic or mixed types, which may reflect limited statistical power in these subgroups.
CONCLUSION: Routine liver function monitoring and age-specific risk assessment are essential for early identification and management of ATB-DILI in hospitalized TB patients.

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PMID: 40303606

Conflict of interest statement: The authors declare that there are no commercial or financial relationships that could be perceived as a potential conflict of interest in relation to this research.

33. Adverse drug reactions and contributing factors in patients with drug-resistant tuberculosis: A 7-year retrospective cohort study in Addis Ababa, Ethiopia.

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BACKGROUND: Drug-resistant tuberculosis poses a major global public health threat, with adverse drug reactions complicating treatment and contributing to mortality. In Ethiopia, although many patients with drug-resistant tuberculosis are receiving treatment, studies on adverse drug reactions and their contributing factors remain limited. This study aimed to assess the incidence of adverse drug reactions and contributing factors in patients on drug-resistant tuberculosis treatment in Addis Ababa, Ethiopia.
METHODS: A facility-based, retrospective cohort study was conducted on patients with drug-resistant tuberculosis who were followed up in two major drug-resistant tuberculosis treatment sites, St. Peter's Specialized Hospital and the ALERT Comprehensive Specialized Hospital, in the years of 2017 to 2023. Records of the patients were reviewed throughout their treatment time. Information on any adverse drug reaction diagnosis, laboratory findings, clinical observations, type of second-line regimen, type and nature of the drug-resistant tuberculosis, presence of comorbidities such as Human Immune deficiency Virus, hypertension, diabetes mellitus, chronic obstructive pulmonary diseases, and asthma, and sociodemographic characteristics were abstracted from patients' charts and registries. The World Health Organization - Uppsala

Monitoring Center (WHO-UMC) system was employed for standardized causality assessment of adverse drug reactions. Multivariate Cox regression analysis was employed to identify factors associated with adverse drug reactions. Survival among predictor variables was assessed using Kaplan-Meier (KM) curves. Adjusted hazard ratios (AHR) with their corresponding 95 % confidence intervals (CI) were estimated, and statistical significance was declared for a p-value < 0.05.
RESULT: A total of 292 patients with drug-resistant tuberculosis were included. The overall incidence of adverse drug reaction was 8.10 per 100 person-month (PM) (95 % CI: 7.02-9.36) during a total follow-up time of 2294 months. The most frequently reported adverse drug reactions were gastrointestinal disturbance (31.9 %), followed by peripheral neuropathy (21.9 %), and arthralgia (17.5 %). Factors associated with adverse drug reactions were hospitalization (AHR = 1.53, 95 % CI: 1.10-2. 13), baseline anemia (AHR = 1.58, 95 % CI: 1.16-2.17), the age group of 25-49 years (AHR = 1.53, 95 % CI: 1.05-2.21), and age greater than or equal to 50 years (AHR = 1.87, 95 % CI: 1.19-2.93). Good treatment outcome was observed in 76 % of cases.
CONCLUSION: In this study involving patients with drug resistant tuberculosis, over half of the participants encountered at least one adverse drug reactions. Patient admission, baseline anemia, and older age were identified as major factors associated with adverse drug reaction during multidrug resistant tuberculosis treatment. Particular emphasis should be placed on these susceptible groups to facilitate early prediction, prompt management, and the formulation of appropriate treatment regimens that address adverse drug reactions effectively.

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

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

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this study.

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

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BACKGROUND: People with multidrug-resistant tuberculosis experience burdensome symptoms, clinical uncertainty, and high mortality. Palliative care is a designated essential health service under Universal Health Coverage. We aimed to test the hypothesis that receipt of additional nurse-led palliative care would improve patient-reported outcomes for patients with multidrug-resistant tuberculosis, compared with usual care.
METHODS: This single-masked, parallel pragmatic randomised controlled trial recruited adults from three public hospitals in Uganda (Mulago National Referral Hospital Kampala, Gulu Regional Referral Hospital, and Mbale Regional Referral Hospital). Inclusion criteria for the study were adults aged 18 years and older with a confirmed bacteriological diagnosis of multidrug-resistant tuberculosis (not responsive to isoniazid or rifampicin) who were registered at the respective study site clinics and who were able to give informed consent. Participants were randomly assigned (1:1) to the intervention (additional nurse-led care) or the standard care control group using randomly permuted blocks stratified by treatment centre. Intervention group participants received nurse-led person-centred holistic assessment, care planning, symptom control, and psychosocial support delivered on inpatient wards or at home. Fortnightly appointments alternated between face-to-face visits and telephone follow-up. Researchers were masked to participant group allocation. The primary outcome was multidimensional palliative care-related symptoms and concerns measured using the African Palliative Care Association Integrated Palliative Outcome Scale,

measured monthly from baseline to the primary 4-month endpoint, analysed using a linear mixed-effect model, applying the intention-to-treat principle to analyse participants by allocated group. The trial was registered on the ISRCTN registry (ISRCTN13664346) and is complete.
FINDINGS: Between Dec 18, 2019, and Sept 10, 2020, 178 individuals were initially assessed for eligibility, 24 were excluded for not meeting inclusion criteria, declining to participate, or being too ill to participate, and 154 participants were recruited and randomly assigned to the intervention group or the control group. 76 were assigned to the nurse-led palliative care group and 78 were assigned to the control group. 52 (34%) participants were female and 102 (66%) were male and participants had an overall median age of 38 years (IQR 31-46). From the linear mixed-effects model the intervention had a significant positive effect compared with standard care (5·12 scale-points [95% CI 2·89-7·21], p<0·0001) at the 4-month follow-up. The standardised effect size was 0·61 (95% CI 0·35-0·86).
INTERPRETATION: Additional nurse-led palliative care for patients with multidrug-resistant tuberculosis improved self-reported outcomes spanning physical, psychological, social, and spiritual domains, and increased medication adherence. Person-centred assessment and holistic care with pain and symptom control should be task-shifted into routine tuberculosis care.
FUNDING: Open Society Foundations.

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PMID: 40412430

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

36. Drug-Induced Lichenoid Photosensitivity: A Case Report.

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Tuberculosis (TB) is a highly contagious airborne bacterial infection and continues to be one of the leading causes of mortality worldwide. First-line antitubercular therapy (ATT), including isoniazid, rifampicin, pyrazinamide, and ethambutol, is essential for TB management but is associated with adverse drug reactions (ADRs), including severe cutaneous manifestations. Managing these ADRs poses significant challenges, as discontinuation of ATT, combined with systemic steroid use, may increase the risk of disease progression and multidrug resistance. Drug-induced lichenoid photosensitivity is an uncommon yet clinically significant skin-related adverse reaction to ATT. Its unpredictable onset and clinical resemblance to autoimmune disorders make early recognition and accurate diagnosis essential to avoid mismanagement or delays in treatment. Timely identification and appropriate intervention are critical not only for minimizing complications but also for maintaining uninterrupted TB therapy. This case report highlights the importance of recognizing and effectively managing drug-induced lichenoid photosensitivity associated with antitubercular agents. We describe a 62-year-old male diagnosed with cervical tuberculous lymphadenitis who developed this rare cutaneous adverse reaction during ATT. The case underscores the need for early diagnosis, individualized treatment strategies, and the vital role of pharmacovigilance in promoting patient safety and ensuring the uninterrupted continuation of TB management.

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PMID: 40406781

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37.Clinical characteristics and genomic epidemiological survey of tuberculosis in Wuzhou, China, 2022.

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Tuberculosis (TB) is a serious respiratory disease posing significant public health threats, such as the variation in Mycobacterium tuberculosis (M.tb) lineages and their associated drug resistance across regions. In 2022, clinical data and culture-positive TB samples were collected from the Third People's Hospital in Wuzhou, China. M.tb drug resistance and lineage were analyzed using whole-genome sequencing, while logistic regression was applied to identify factors influencing patient outcomes. Among 169 strains analyzed, an overall drug resistance rate of 23.1% was observed. Multidrug-resistant or rifampicin-resistant cases constituted 7.7% of the strains. Most strains belonged to lineage 2 (69.8%), followed by lineage 4 (27.8%). Poor treatment adherence, being aged 65 or older, and retreatment emerged as risk factors for unfavorable outcomes. This pioneering survey provides crucial insights into TB patient characteristics, drug resistance patterns, and lineage distribution in Wuzhou, laying a foundation for future targeted TB control strategies in the region.IMPORTANCEIn 2022, tuberculosis (TB) was the second leading cause of death from a single infectious agent worldwide, posing a serious threat to global health. The epidemiological characteristics of TB vary considerably from country to country, and even from region to region within a single country, due to differences in the economy, medical conditions, education, and other factors. Understanding the current status of TB epidemics in the region is important, with practical implications for local diagnosis, treatment, and control. This genomic epidemiological survey has provided a first insight into the characteristics of TB patients, drug resistance rates, prevalence lineage, and factors associated with unfavorable outcomes in Wuzhou, China.

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PMID: 40207933 [Indexed for MEDLINE]

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

38. Comparative evaluation of five β-Lactamase inhibitors in combination with β-Lactams against multidrug-resistant Mycobacterium tuberculosis in vitro.

BMC Infect Dis. 2025 Apr 28;25(1):619. doi: 10.1186/s12879-025-10730-y.

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OBJECTIVE: Evaluating the activity of six β-lactams in combination with different β-lactamase inhibitors to identify the most potent combination against Mycobacterium tuberculosis(MTB) in vitro.
METHODS: A total of 105 MDR-TB strains from different regions of Henan province were included in this study.Drug susceptibility of sixβ-lactams alone or in combination with β-lactamase inhibitors was examined by broth dilution method against 105 clinical isolates.Mutations of blaC, ldtmt1,dacB2and ldtmt2 were analyzed by PCR and DNA sequencing.
RESULTS: Out of the β-lactams used herein, tebipenem was the most effective against MDR-TB and had an MIC90 value of 16 μg/ml.Clavulanic acid, tazobactam, and sulbactam, demonstrated the best synergy with tebipenem, resultingin an 32-fold reduction in theMIC values for 12, 5, and 20 strains, respectively. Simultaneously, these three types ofβ-lactamase inhibitors had the least impact on imipenem.Clavulanic acid caused the maximum 8-fold reduction in the MIC value of imipenem, while tazobactam and sulbactam only resulted in the maximum 4-fold reduction in the MIC value of imipenem. Besides, after the addition ofβ-lactamase inhibitors, the MICs of most β-lactam drugs were reduced more evidently in the presence of avibactamand tazobactamcompared to other β-lactamase inhibitors. In addition, 13.33% (14/105) of isolates harbored mutations in the blaC gene, with three different nucleotide substitutions: AGT333AGG 、AAC638ACCand ATC786ATT. For the strains with a Ser111Arg andAsn213Thrsubstitution inBlaC, a better synergistic effect was observed in the meropenem-clavulanate and in the meropenem-sulbactam combinationsthan that in a synonymous single nucleotide polymorphism (SNP) group.
CONCLUSION: the combination of tebipenem and relebactam shows the most potent activity against MDR-TB isolates. In addition, the Ser111Arg and Asn213Thr substitution of BlaC may be associated with increased susceptibility of MDR-TB isolates to meropenem in thepresence of clavulanate and sulbactam.

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Conflict of interest statement: Declarations. Ethics approval and consent to participate: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Medical Ethics Committee of the Henan Provincial Center for Disease Control and Prevention(Number: 2023-KY-002-02).Informed consent was obtained from all subjects involved in the study. Consent for publication: Not applicable. Clinical trial: Not applicable. Competing interests: The authors declare no competing interests.

39. Severity and associated factors of anaemia among rifampicin/multi-drug-resistant tuberculosis patients treated in Alert and St. Peters specialised hospitals, Addis Ababa, Ethiopia: a retrospective cross-sectional study.

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OBJECTIVE: To assess the severity of anaemia and associated factors among drug-resistant tuberculosis (DR-TB) patients treated in DR-TB treatment-initiating centers in Addis Ababa, Ethiopia.
DESIGN: A retrospective cross-sectional study.
SETTINGS: This study was conducted in Alert and St. Peters specialised hospitals, Addis Ababa, from 20 September to 15 October 2022.
METHODS AND ANALYSIS: Data was collected from 331 patients with DR-TB. The data was entered into Epi-Data 4.1, and SPSS version 25 was used for data cleaning and analysis. A multinomial logistic regression model was fitted after the multi-collinearity assumptions, and goodness-of-fit tests were done. The OR with 95% CI was reported for each outcome variable, taking normal haemoglobin level as a reference category. Variables with a P value of <0.05 were considered

statistically significant.
RESULTS: Of the 331 patients, 51.4% had baseline anaemia, of which 5.7%, 15.7% and 29.9% had severe, moderate and mild anaemia, respectively.Patients who were urban residents (AOR: 0.06, 95% CI: 0.012, 0.32), government employees (AOR: 0.33, 95% CI: 0.001, 0.79), private job holders (AOR: 0.02, 95% CI: 0.001, 0.27), undernourished (AOR: 15.72, 95% CI: 2.46, 100.28), patients with HIV (AOR: 7.28, 95% CI: 1.627, 32.628) and farmers and students (AOR: 0.05, 95% CI: 0.004, 0.58) were significantly associated with severe anaemia.Patients who were male (AOR: 0.31, 95% CI: 0.11, 0.93), single (AOR: 0.19, 95% CI: 0.04, 0.85), daily labourer (AOR: 6.19, 95% CI: 1.27, 30.2), undernourished (AOR: 12.83, 95% CI: 4.88, 33.7) and patients with HIV (AOR: 12.74, 95% CI: 4.67, 34.75) were significantly associated with moderate anaemia. Patients with undernutrition (AOR: 3.92, 95% CI: 2.1, 7.35), HIV (AOR: 2.79, 95% CI: 1.22, 6.39) and primary and secondary education (AOR: 0.36, 95% CI: 0.17, 0.77) were significantly associated with mild anaemia.
CONCLUSION: In our study, more than 50% of patients with DR-TB had baseline anaemia, of which mild anaemia was the most common typeanaemia. Rural residents were at a higher risk of developing severe anaemia (11.5%), while the overall rate of anaemia (58.8%) was higher among urban residents.

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Conflict of interest statement: Competing interests: None declared.

40. The effects of stigma and social support on the health-related quality of life of people with drug resistance tuberculosis in Lagos, Nigeria.

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PURPOSE: This study assessed the effects of TB stigma and social support on the health-related quality of life (HRQoL) of people living with drug-resistant tuberculosis (DR-TB) in Lagos, Nigeria.
METHODS: A cross-sectional study was conducted in five DR-TB treatment centres in Lagos, Nigeria, between September and December 2023. A total of 203 adults on DR-TB treatment were recruited to complete a questionnaire including the Redwood DR-TB stigma scale, the Functional Assessment of Chronic Illness Therapy-TB (FACCIT) scale, and the Multidimensional Scale of Perceived Social Support (MSPSS). Student 't' test/one-way ANOVA, Pearson's correlation, and hierarchical linear regression analysis were conducted to explore the factors associated with HRQoL and the relationships between stigma, social support, and HRQoL.
RESULTS: The mean overall HRQoL was 41.1 ± 12.9 among people with DR-TB. The HRQoL score of the physical domain was the lowest (25.8 ± 13.8). Participants who were young, male, single, with higher education, and HIV-negative had higher HRQoL than their counterparts ($p < 0.05$). Stigma was negatively associated with HRQoL, while social support was positively related, collectively explaining 57.6% of the variance. In the final model, social support contributed more ($B = 0.576$) to predicting HRQoL than did stigma ($B = - 0.414$).
CONCLUSION: The overall HRQoL of people with DR-TB in Lagos, Nigeria, was poor. Strategies that improve social support systems and reduce stigma are needed to improve this. Further studies are also required to assess the changes in HRQoL over time and evaluate the impact of specific stigma-reduction interventions.

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PMID: 39964366 [Indexed for MEDLINE]

Conflict of interest statement: Declarations. Conflict of interest: The authors have no relevant financial or non-financial interests to disclose. Ethical approval: This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Health Research and Ethics Committee of the Lagos State University Teaching Hospital (LREC/06/10/2179) and the Institutional Research Ethic Committee of Durban University of Technology, South Africa (IREC 066/230). Gatekeepers’ permission to interview participants was obtained from the Lagos State Ministry of Health and the medical directors of the DR-TB treatment centres where participants were recruited. Informed consent: A written informed consent was obtained from all participants included

in the study. The objectives of the study were explained to the participants. They were also informed that participation or non-participation in the study would not affect the provision of healthcare services. In addition, they were informed that they were free to withdraw their consent at any time during the study. The data was anonymized, and personal identifiers were not obtained.

41. Proteomic characterization of Mycobacterium tuberculosis subjected to carbon starvation.

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Update of
bioRxiv. 2024 Nov 12:2024.11.12.623260. doi: 10.1101/2024.11.12.623260.

Mycobacterium tuberculosis (Mtb) is the causative agent of tuberculosis (TB), the leading cause of infectious disease-related deaths worldwide. TB infections present on a spectrum from active to latent disease. In the human host, Mtb faces hostile environments, such as nutrient deprivation, hypoxia, and low pH. Under these conditions, Mtb can enter a dormant, but viable, state characterized by a lack of cell replication and increased resistance to antibiotics. Dormant Mtb poses a major challenge to curing infections and eradicating TB globally. We subjected Mtb mc26020 (ΔlysA and ΔpanCD), a double auxotrophic strain, to carbon starvation (CS), a culture condition that induces growth stasis and mimics environmental conditions associated with dormancy in vivo. We provide a detailed analysis of the proteome in CS compared to replicating samples. We observed extensive proteomic reprogramming, with 36% of identified proteins significantly altered in CS. Many enzymes involved in oxidative phosphorylation and lipid metabolism were retained or more abundant in CS. The cell wall biosynthetic machinery was present in CS, although numerous changes in the abundance of peptidoglycan, arabinogalactan, and mycolic acid biosynthetic enzymes likely result in pronounced remodeling of the cell wall. Many clinically approved

anti-TB drugs target cell wall biosynthesis, and we found that these enzymes were largely retained in CS. Lastly, we compared our results to those of other dormancy models and propose that CS produces a physiologically distinct state of stasis compared to hypoxia in Mtb.IMPORTANCETuberculosis is a devastating human disease that kills over 1.2 million people a year. This disease is caused by the bacterial pathogen Mycobacterium tuberculosis (Mtb). Mtb excels at surviving in the human host by entering a non-replicating, dormant state. The current work investigated the proteomic changes that Mtb undergoes in response to carbon starvation, a culture condition that models dormancy. The authors found broad effects of carbon starvation on the proteome, with the relative abundance of 37% of proteins significantly altered. Protein changes related to cell wall biosynthesis, metabolism, and drug susceptibility are discussed. Proteins associated with a carbon starvation phenotype are identified, and results are compared to other dormancy models, including hypoxia.

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PMID: 40231840 [Indexed for MEDLINE]

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

42. Detection of extensive drug resistance by the Xpert MTB/XDR assay in multidrug resistant tuberculosis cases at a tertiary care centre in northern India, and therapeutic decision making for the six-month BPaLM regimen.

J Clin Tuberc Other Mycobact Dis. 2025 Mar 21;39:100520. doi: 10.1016/j.jctube.2025.100520. eCollection 2025 May.

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The Xpert MTB/XDR assay has been approved by World Health Organization (WHO) as a reflex test on sputum samples after testing for rifampicin resistance. Recently, the Union Health Ministry of India in September 2024 approved the

introduction of the six-month BPaLM regimen under its National TB Elimination Program (NTEP). In this study, the Xpert MTB/XDR assay was used to detect extensive drug resistance in pulmonary and extra-pulmonary tuberculosis patients with positive result for MTBC, and RIF resistance by the Xpert MTB/RIF ULTRA assay. We also aimed to assess the eligibility of patients for the BPaLM regimen based on the drug susceptibility profile of this test in a high burden Indian setting. We conducted a single centre prospective cohort study between January 2023 to August 2024 on 42 old, and 68 new patients presenting with MDR/RR tuberculosis. A total of 110 samples (82 pulmonary and 28 extra pulmonary samples) were included in the study. The Xpert MTB/XDR assay was used to determine the susceptibilities to isoniazid, fluoroquinolones, amikacin, kanamycin, capreomycin, and ethionamide. Out of 110 samples processed, 13 samples were 'not detected' by the assay while three gave invalid results. Resistance to isoniazid, fluoroquinolones, amikacin, kanamycin, capreomycin and ethionamide was detected in 85/94 cases (90·42%), 74/94 cases (78·72%), 08/94 cases (8·5%), 13/94 cases (13·83%), 08/94 cases (8·5%), and 14/94 cases (14·89%) respectively. With the updated definitions of drug-resistant TB and high burden of fluoroquinolone resistance the Xpert MTB/XDR assay has a limited application in India. Detection of extensive drug resistance by the Xpert MTB/XDR assay in multidrug resistant tuberculosis cases at a tertiary care centre in northern India, and therapeutic decision making for the six-month BPaLM regimen.

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PMID: 40225357

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

43. Treatment outcomes and key factors contributing to unfavourable outcomes among isoniazid-resistant pulmonary tuberculosis patients in Shanghai, China.

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OBJECTIVE: Given that more than 1 million people annually develop isoniazid-resistant tuberculosis (Hr-TB), the issue of Hr-TB may go unnoticed. However, limited studies have focused on the clinical treatment of Hr-TB in China, particularly regarding treatment outcomes and influencing factors. This study aimed to evaluate the treatment outcomes of Hr-TB patients in Shanghai from 2018 to 2021 and analyse the influencing factors, including demographic characteristics, clinical features, and treatment-related factors.
METHODS: This study retrospectively reviewed the medical records of Hr-TB patients registered in the TB management information system from 2018 to 2021. Differences in demographic characteristics, clinical information, and treatment outcomes were evaluated. Multivariable logistic regression was used to identify risk factors associated with unfavourable outcomes.
RESULTS: A total of 664 patients with Hr-TB were included in the analysis. A total of 84 cases (12.7%) had unfavourable outcomes. Only 318 (47.9%) Hr-TB patients used regimens containing fluoroquinolones. Adverse events occurred in 127 cases (19.1%), of which 12 cases (1.81%) discontinued treatment due to adverse events. There was statistically significant difference in the occurrence of adverse events between the different treatment regimens ($P < 0.001$). Multivariable logistic regression showed that older age (adjusted odds ratio = 6.13, 95% confidence intervals [CI] = 1.24-30.24, $P = 0.026$), use of injectable agents (adjusted odds ratio = 3.75, 95% CI = 1.29-10.94, $P = 0.016$), and treatment duration (95% CI = 21.85-1487.61, $P < 0.001$) were risk factors for unfavourable treatment outcomes.
CONCLUSIONS: Unfavourable outcomes were more frequent among older patients and those receiving injectable agents among Hr-TB patients in Shanghai, a low-endemic region for TB. This emphasizes the need for timely diagnosis and optimized treatment strategies for isoniazid-resistant tuberculosis.

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PMID: 40023221 [Indexed for MEDLINE]

44. Model-Informed Once-Daily Dosing Strategy for Bedaquiline and Delamanid in Children, Adolescents and Adults with Tuberculosis.

Clin Pharmacol Ther. 2025 May;117(5):1292-1302. doi: 10.1002/cpt.3536. Epub 2024 Dec 28.

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The complexity of the currently registered dosing schedules for bedaquiline and delamanid is a barrier to uptake in drug-resistant tuberculosis treatment across all ages. A simpler once-daily dosing schedule is critical to ensure patient-friendly regimens with good adherence. We assessed expected drug exposures with proposed once-daily doses for adults and compared novel model-informed once-daily dosing strategies for children with current World Health Organization (WHO) recommended dosing. A reference individual and virtual pediatric population were generated to simulate exposures in adults and children, respectively. Published population models characterizing the exposures of bedaquiline and its metabolite M2, delamanid, and its metabolite DM-6705 were utilized. During simulation, child growth during treatment along with several CYP3A4 ontogeny profiles was accounted for. Exposures in children were compared with simulated adult targets to assess the expected treatment efficacy and safety. In adults, the proposed bedaquiline once-daily dosing (400 mg daily for 2 weeks followed by 100 mg daily for 22 weeks) yielded 14% higher exposures of bedaquiline and M2 compared to the labeled dosing scheme at 24 weeks; for delamanid and DM-6705, the suggested 300 mg daily dose provided 13% lower exposures at steady state. For children, the cumulative proportions of exposures of both drugs showed < 5% difference between WHO-recommended and proposed once-daily dosing. This study demonstrated the use of model-informed approaches to propose rational and simpler regimens for bedaquiline and delamanid in adults and children. The new once-daily dosing strategies will be tested in the PARADIGM4TB and IMPAACT 2020 trials in adults and children, respectively.

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Conflict of interest statement: E.M.S. and M.O.K. have received research grants from Janssen Pharmaceuticals. All other authors declared no competing interests for this work.

45.Impact of malnutrition and associated factors on rifampicin/multi-drug-resistant tuberculosis treatment outcomes among patients treated in alert and St. Peter's Specialized Hospitals, Addis Ababa, Ethiopia: a retrospective follow-up study.

BMC Res Notes. 2025 May 6;18(1):204. doi: 10.1186/s13104-025-07268-2.

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OBJECTIVE: This study was aimed to assess the impact of malnutrition and associated factors on rifampicin/multi-drug-resistant tuberculosis treatment outcomes among patients treated in Alert and St. Peter's Specialized Hospitals, Addis Ababa, Ethiopia.
RESULTS: Our study included 344 RR/MDR-TB patients, of which 43.3% were undernourished. The overall unsuccessful treatment outcome was 22.1% (95% CI 0.18, 0.27). Patients with undernutrition were over eight times more likely to develop unsuccessful treatment outcomes [AOR = 8.32 (95% CI 4.48, 15.46)] compared to normal/ overweight individuals. After we computed the binary logistic regression analysis separately for patients with undernutrition and normal/ overweight nutritional status, age, residence, occupation, chest x-ray,

anemia, co-morbidities, cigarette smoking, and alcohol drinking were significantly associated with unsuccessful treatment outcomes among undernourished patients, while age, HIV, and smoking were significantly associated with unsuccessful treatment outcomes among patients with normal/overweight individuals.
CONCLUSIONS: In this study, undernutrition had a remarkable impact on unsuccessful treatment outcomes. Therefore, further researches need to be conducted to integrate the management of undernutrition with the DR-TB treatment program.

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PMCID: PMC12057184
PMID: 40329314 [Indexed for MEDLINE]

Conflict of interest statement: Declarations. Ethical approval and consent to participate: Ethical clearance was obtained from University of Gondar Ethical Reviewed Board (UoG IRB). Furthermore, the ethical clearance was presented to medical directors of both Alert and St. Peter's Specialized Hospitals. Data collection was started after oral informed consent was obtained medical director of each hospital. All the information collected was kept confidential. In general, this study was conducted according to ethical principles of the declaration Helsinki, 1964. Competing interests: The authors declare no competing interests.

46. Unprecedented in vivo activity of telacebec against Mycobacterium leprae.

PLoS Negl Trop Dis. 2025 May 8;19(5):e0013076. doi: 10.1371/journal.pntd.0013076. eCollection 2025 May.

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BACKGROUND: New drugs targeting the electron transport chain (ETC) seem to be a promising advance in leprosy treatment. In this study, we evaluated the bactericidal activity of telacebec (TCB), a phase 2 drug candidate for tuberculosis, alongside known ETC-targeting antibiotics, bedaquiline (BDQ) and clofazimine (CFZ), as monotherapy or in combination.
METHODOLOGY/ PRINCIPAL FINDINGS: We used the reference leprosy proportional bactericidal mouse footpad model. Four hundred and ten mice were inoculated in the footpads with 5x104 to 5x100 bacilli of M. leprae strain THAI53 for the untreated control group and groups treated with drug-monotherapies, and with 5x104 to 5x101 for groups treated with drug-combinations. Mice were randomly allocated into the following groups: 2 control groups (untreated or standard multi drug therapy (MDT), rifampin, dapsone and clofazimine with dosing equipotent to human dosing) and 7 test groups (TCB 10mg/kg, bedaquiline 25mg/kg (BDQ), clofazimine 20mg/kg (CFZ), CFZ + BDQ, TCB + BDQ, TCB + CFZ, TCB + CFZ + BDQ). Mice in the test groups received either one month treatment (MDT) or a single dose of the drugs (TCB, RIF, BDQ, CFZ). Twelve months later, mice were sacrificed to enumerate M. leprae bacilli in the footpad. All the footpads became negative in the MDT, TCB and combination groups except in the TCB + CFZ group where 2 mice remained positive in the 5x104 inoculum.
CONCLUSION: We demonstrated that monotherapy of TCB exhibited bactericidal activity against M. leprae comparable to that of MDT and that all combination therapies were as effective as MDT, except the combination TCB + CFZ, possibly due to an antagonism between these two drugs.

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PMCID: PMC12061105
PMID: 40338896 [Indexed for MEDLINE]

Conflict of interest statement: We have read the journal's policy and the authors of this manuscript have the following competing interests: - AC, NV and AA are part of the Respiri-TB project in collaboration with Janssen pharmaceutica. - VJ and KP have declared that no competing interests exist.

47. The antibacterial activity and therapeutic potential of the amphibian-derived peptide TB_KKG6K.

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Antimicrobial peptides (AMPs) have great potential to be developed as topical treatments for microbial infections of the skin, including those caused by the gram-positive human pathogen Staphylococcus aureus. Among the AMPs, temporin B (TB) is of particular interest. This 13-amino-acid-long cationic peptide is secreted by the granular glands of the European frog Rana temporaria and represents a primary line of defense against invading pathogens. The objective of this study was to investigate the antibacterial efficacy and the mode of action of the synthetic TB analog, TB_KKG6K, in a drug-resistant clinical isolate of S. aureus and assess the peptide's tolerance and curative potential in an in vitro infection model using three-dimensional human epidermis equivalents (HEEs). The results revealed a high bactericidal efficacy of TB_KKG6K at low micromolar concentrations. The peptide perturbed the bacterial cell membrane integrity by permeabilization and depolarization. TB_KKG6K showed no toxicity in the invertebrate mini-host model Galleria mellonella and a high level of tolerance when topically applied in HEEs. Importantly, the therapeutic potential of TB_KKG6K was confirmed in HEEs infected with S. aureus. The topical application of TB_KKG6K significantly reduced the bacterial load and lowered the pro-inflammatory response in the infected HEEs. These findings reinforce the antibacterial potential and therapeutic efficacy of TB_KKG6K against S. aureus infection, particularly in the context of a cutaneous infection.IMPORTANCEThe emergence of multidrug-resistant bacteria has rendered the exploration of novel therapeutic treatment strategies a pivotal area of research. Among the most promising candidates are amphibian-derived antimicrobial peptides (AMPs), which are ideal for the development of novel drugs due to their multifaceted mode of

action. Extensive studies have been conducted on these peptides over the last decade, resulting in the development of temporin B (TB) peptide analogs that have undergone modifications to their primary sequence. These modified analogs have demonstrated enhanced antibacterial and antifungal efficacy, while exhibiting reduced hemolytic activity. TB_KKG6K has the potential to be a promising candidate for topical treatments due to its small size and high antimicrobial activity against pathogens of the human skin. In particular, it demonstrated efficacy against Staphylococcus aureus, a skin commensal that can become an opportunistic pathogen, causing a range of infections from minor skin infections to life-threatening diseases such as bacteremia and sepsis.

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PMID: 40387366

48. Structural isomerisation affects the antitubercular activity of adamantyl-isoxyl Adducts.

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Despite efforts to discover effective treatments to eradicate tuberculosis (TB), it remains a global threat. The increase in drug-resistant bacterial species has made the discovery of new drugs highly coveted. The utilisation of previous efficacious structures is one approach that can be employed to developing novel series of compounds to combat this ever-growing problem. This study sought to re-examine two such compounds, isoxyl (ISO) and SQ109, previously shown to be efficacious in TB treatment. SQ109-ISO hybrid compounds were shown to have demonstrable activity against both drug-sensitive and drug-resistant Mtb whilst displaying limited toxicity in vitro in comparison to other antitubercular

agents. Indications from our genetic and biochemical studies suggest that these structurally similar pharmacophores bind to different proteins within Mtb, highlighting the need for careful consideration when producing regioisomeric analogues and that the utilisation of previous efficacious structures is a valid approach to developing promising novel drugs against Mtb.

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PMID: 40396606 [Indexed for MEDLINE]

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

49.Epidemiological insights into paediatric tuberculosis trends in the Western Cape, South Africa.

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BACKGROUND AND OBJECTIVES: Paediatric tuberculosis (TB) remains a major public health concern in high-burden settings like the Western Cape (WC), South Africa.

We analysed geographic differences in TB burden among children and adolescents, described temporal trends, and quantified gaps in the TB care cascade.
METHODS: We analysed TB episodes recorded in the WC Provincial Health Data Centre (PHDC) from 2017-2023, stratified by 5-year age groups, and compared them to adult episodes. We assessed HIV status, drug resistance status, microbiological testing, disease classification, place of diagnosis, and TB treatment outcomes. Reporting gaps were estimated by comparing PHDC-recorded episodes to national notifications. Incidence rates were calculated using mid-year population estimates.
RESULTS: In 2023, TB incidence rates of diagnosis in the WC were 722.4, 189.1, 171.2, and 523.4 per 100,000 population ages 0-4, 5-9, 10-14, and 15-19 years. Children aged 0-4 years accounted for 47.9% of paediatric TB episodes. In the Cape Winelands district in 2023, TB incidence among 0-4-year-olds was double that of adults in the district and 2-4 times higher than 0-4-year-olds in other districts. Among PHDC-recorded episodes, 17.3% were not reported at national level. Treatment success was low, with only 70.3% of diagnosed children and adolescents completing treatment in 2023.
CONCLUSIONS: Our findings highlight geographic variation in paediatric TB burden in the WC, emphasizing the need to address local drivers to inform targeted interventions. Gaps in the paediatric TB care cascade remain major concerns. Strengthening integrated data systems beyond TB treatment registers, could improve surveillance, health system planning, and patient outcomes.

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50.Beta-lactam combination treatment overcomes rifampicin resistance in Mycobacterium tuberculosis.

Eur J Clin Microbiol Infect Dis. 2025 May;44(5):1279-1284. doi: 10.1007/s10096-025-05062-3. Epub 2025 Mar 6.

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The significant global impact of tuberculosis (TB) on human health is exacerbated by the increasing prevalence of multi-drug resistant tuberculosis (MDR-TB) and the challenges of novel drug discovery for the treatment of drug-susceptible and drug-resistant strains of M. tuberculosis. Rifampicin is a key first-line TB drug and rifampicin resistance is a major obstacle to treating MDR-TB. Utilising existing antimicrobial drugs to supplement combination therapy and overcome rifampicin resistance is a promising solution due to their widespread availability and proven clinical safety profile. Therefore, this study aimed to explore the feasibility of using beta-lactam/beta-lactamase inhibitor combinations with rifampicin to inhibit the growth of multidrug-resistant M. tuberculosis. Based on inhibitory concentration (IC), oral bioavailability, pricing, commercial availability, five beta-lactams and the beta-lactamase inhibitor, clavulanate, were selected for testing. These were combined with rifampicin for in vitro testing against Mycobacterium tuberculosis H37Rv. Resazurin assays and colony forming unit (CFU) enumeration were used to quantify drug efficacy, Chou-Talalay calculations were performed to identify drug synergy and Chou-Martin calculations were performed to quantify drug dose reduction index (DRI). The combination of tebipenem-clavulanate/rifampicin and cephradine-clavulanate/rifampicin were found to be synergistic and highly effective against clinical isolates of MDR-TB, overcoming rifampicin resistance in vitro. Beta-lactam synergy may provide viable combination therapies with rifampicin to address the issue of drug resistance in TB.

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PMID: 40048098 [Indexed for MEDLINE]

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Competing interests: The authors declare no competing interests.

51. Diagnostic yield of nine user-friendly bioinformatics tools for predicting Mycobacterium tuberculosis drug resistance: A systematic review and network meta-analysis.

PLOS Glob Public Health. 2025 Apr 21;5(4):e0004465. doi: 10.1371/journal.pgph.0004465. eCollection 2025.

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To compare the diagnostic yield of various bioinformatics tools for predicting Mycobacterium tuberculosis drug resistance. A systematic review of PubMed, Embase, Scopus, Web of Science, CINAHL and the Cochrane Library was performed to identify studies reporting the effectiveness of bioinformatic tools for predicting resistance to anti-tuberculosis (TB) drugs. Data were collected and pooled using random-effects meta-analysis and Bayesian network meta-analysis (NMA). Summary receiver operating characteristic curves (SROCs) analysis were performed, and superiority index (SI) and area under the curve (AUC) were calculated. Thirty-three studies evaluated 9 different bioinformatics tools for predicting resistance to 14 anti-TB drugs. NMA and SROCs demonstrated that TBProfiler, TGS-TB, Mykrobe, PhyResSE, and SAM-TB all exhibited satisfactory performance. Remarkably, TBProfiler stood out with its exceptional ability to predict resistance to the majority of anti-TB drugs, including isoniazid (SI: 3.39 [95% confidence interval (CI): 0.20, 11.00]; AUC: 0.97 [0.95, 0.98]), rifampicin (SI: 6.38 [0.60, 15.00]; AUC: 0.99 [0.98, 1.00]), ethambutol (SI: 5.15 [0.60, 13.00]; AUC: 0.96 [0.94, 0.97]), streptomycin (SI: 3.67 [0.60, 11.00]; AUC: 0.97 [0.95, 0.98], amikacin (SI: 2.49 [0.14, 11.00]; AUC: 0.97 [0.96, 0.99]), kanamycin (SI: 2.26 [0.14, 9.00]; AUC: 0.98 [0.97, 0.99]), levofloxacin (SI: 1.87 [0.11, 9.00]; AUC: 0.95 [0.93, 0.97]), and prothionamide

(SI: 2.73 [0.20, 7.00]; AUC: 0.87 [0.84, 0.90]). Meanwhile, Mykrobe demonstrated superior accuracy specifically for moxifloxacin (SI: 3.96 [0.11, 13.00]; AUC: 0.97 [0.95, 0.98]). Lastly, TGS-TB had the best efficacy in predicting resistance to pyrazinamide (SI: 12.53 [1.67, 17.00]; AUC: 0.97 [0.95, 0.98]), capreomycin (SI: 4.22 [0.08, 15.00]; AUC: 1.00 [0.98, 1.00]), and ethionamide (SI: 2.15 [0.33, 7.00]; AUC: 0.96 [0.94, 0.98]). TBProfiler, TGS-TB, Mykrobe, PhyResSE and SAM-TB have all demonstrated outstanding accuracy in predicting resistance to anti-TB drugs. In particular, TBProfiler stood out for its exceptional performance in predicting resistance to most anti-TB drugs, while TGS-TB excelled in predicting resistance to pyrazinamide and certain second-line drugs. The efficacy of SAM-TB requires further investigation to fully establish its reliability and effectiveness. To ensure the accuracy and reliability of genotypic drug susceptibility testing, bioinformatics tools should be refined and adapted continuously to accommodate novel and current resistance-associated mutations.

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PMID: 40258039

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

52. Genomic-based genotype and drug susceptibility profile of Mycobacterium kansasii in China.

Front Microbiol. 2025 Apr 29;16:1573448. doi: 10.3389/fmicb.2025.1573448. eCollection 2025.

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To analyze subtypes, microbiological characteristics and antimicrobial susceptibility of Mycobacterium kansasii in China, a total of 153 M. kansasii isolates, collected from national drug resistance surveillance, were genotyped with whole genome sequencing and explored the antimicrobial susceptibility with broth microdilution. All isolates were classified as M. kansasii type I based on Average Nucleotide Identity(ANI). The 153 M. kansasii representatives were differentiated into 3 clusters with 141 genotypes, including 17 isolates from a cluster and 136 isolates with unique patterns. The EXS-1, EXS-3 and EXS-5 regions were involved in all isolates. Rifabutin and clarithromycin were the most highly active against M. kansasii strains, with the susceptible rate of 100 and 99.35%, respectively. Followed by amikacin and linezolid, the resistance rate was 5.88 and 7.19%, respectively. The resistance rate to rifampin (RIF) was 22.22%. As for the antibiotics without the breakpoint values, all isolates had very low MIC50 (0.03 μg/mL) and MIC90 (≤0.06 μg/mL) values against bedaquiline, sutezolid, delamanid, and clofazimine. Except for ciprofloxacin and moxifloxacin, the resistance rate of other drugs in cluster 3 was higher than that in cluster 1 and cluster 2. In conclusion, M. kansasii type I was the predominant genotype in China, and rifabutin and clarithromycin presented strong activities. The new drugs, used for the treatment of multidrug - resistant tuberculosis, have the potential to be potent agents in the treatment of M. kansasii infection. The clustering might contribute to the high resistance rate of M. kansasii.

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PMID: 40365070

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53. Non-inferiority stepped wedge cluster randomized controlled trial on all-oral shorter regimens for rifampicin resistant/multidrug-resistant TB in Pakistan - a

study protocol.

BMC Infect Dis. 2025 May 7;25(1):674. doi: 10.1186/s12879-025-11068-1.

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INTRODUCTION: Pakistan has one of the largest burdens of rifampicin-resistant/multidrug-resistant TB according to the global estimates. Novel all oral treatment regimens containing new antibiotics with reduced treatment duration are available. World Health Organization guidelines recommend the use of shorter all-oral regimens under operational research. To guide recommendations, we will compare two all-oral, short (≤ 11 months) regimens for the outcomes of efficacy, safety, cost, and health-related quality of life under programmatic conditions in Pakistan.
METHODS: This is a stepped wedge, cluster randomized controlled trial with economic evaluation and health related quality of life sub-studies. Modified all-oral 9-month regimen will be sequentially rolled-out compared with the standard all-oral 11-month regimen at 12 sites in Punjab, Islamabad and Azad Jammu and Kashmir region, Pakistan. A total of 400 eligible participants will be enrolled in both study arms. The primary outcome is difference in efficacy as measured by the proportion of patients with treatment success without recurrence at 12 months after the end of treatment between regimens using a non-inferiority design with a margin of 12%. The intention to treat analysis principle will be employed and a marginal mean model with Poisson generalized estimation equations, and a log-link will be used to assess the relative risk. The economic evaluation will be carried out from the healthcare providers perspective; linear mixed models will be used to estimate differences in costs between arms. Health

related quality of life will be measured with the EQ-5D-3L quality of life questionnaire at four time points during the study period. The impact will be assessed by calculating the changes for each participant between time points. Ethical approval for this study has been obtained from national bioethics committee, Pakistan (Ref: No.4-87/NBC-491/20/48).
DISCUSSION: The study's findings will be disseminated to physicians, program implementers, scientific audiences, and policymakers on both a national and international level via reports, presentations, and scientific publications.
TRIAL REGISTRATION: ISRCTN registry. ISRCTN17334530, 'retrospectively registered' on 8th February 2021. 'Clinical trial number: not applicable.'

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PMCID: PMC12060332
PMID: 40335894 [Indexed for MEDLINE]

Conflict of interest statement: Declarations. Ethics approval and consent to participate: The research protocols were submitted for approval by National Bioethics Committee, Pakistan and ethical approval for conducting this study was received (Ref: No.4–87/NBC-491/20/48). Protection of patient confidentiality is essential, and the study will follow the principles of the 2018 Declaration of Helsinki. Informed written consent will be obtained from patients or a guardian in the case of minors, as defined by local legal requirements. Those who do not consent to participate in this research will receive treatment as per national guidelines. Consent for publication: This is a study protocol, does not require consent to publish, Not applicable. Competing interests: The authors declare no competing interests.

54. Treatment success rate and time to culture conversion under a prospective BPaL cohort study.

IJTLD Open. 2025 May 12;2(5):284-290. doi: 10.5588/ijtldopen.24.0524. eCollection 2025 May.

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BACKGROUND: In July 2022, Indonesia implemented the 6-month BPaL (bedaquiline, pretomanid, linezolid) regimen under operational research (OR) for selected drug-resistant tuberculosis patients. The study aimed to assess treatment success rate (TSR) and time to sputum culture conversion (TSCC).
METHODS: A prospective cohort study in fifteen sites between July 2022 and March 2023 enrolled patients with rifampicin-resistant/multidrug-resistant TB with additional fluoroquinolone resistance or intolerance/failures of previous second-line TB treatment. TSR was descriptively analysed, and Kaplan-Meier and Cox proportional-hazards analyses were used to evaluate TSCC.
RESULTS: A total of 87 patients were enrolled, 3 were withdrawn, and 84 completed treatment and had outcomes; 82 (97.6%) patients had successful treatment, 1 (1.2%) died, and 1 (1.2%) had failure. Overall, 61 (72.6%) patients had positive cultures at baseline, and favourable outcomes were included in the TSCC analysis; all 61 (100%) converted within the first 3 months (median 32 days of treatment, IQR 30.0-56.0). None of the six variables were statistically associated with conversion time.
CONCLUSION: The Indonesian BPaL OR showed a highly promising TSR of 97.6%, with 100% sputum conversion within 3 months. The lack of observed statistical differences in the TSCC across variables shows that the BPaL treatment will be equally effective in all patient groups.

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PMCID: PMC12068447
PMID: 40365023

55. Molecular Docking and Molecular Dynamics Study of Propolis Compounds of Sulabiroin-A, Sulabiroin-B, and Broussoflavonol F Toward Tuberculosis 3PTY Target Protein.

J Trop Med. 2025 Apr 30;2025:6631193. doi: 10.1155/jotm/6631193. eCollection 2025.

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Molecular docking and molecular dynamics simulations were conducted to assess propolis compounds of sulabiroin-A, sulabiroin-B, and broussoflavonol F as tuberculosis (TB) inhibitors with rifampicin as the control ligand. TB remains a significant world health concern, requiring the development of new drug candidates to address more drug-resistant variants. The target protein chosen was 3PTY. The molecular docking simulation showed that sulabiroin-A, sulabiroin-B, and broussoflavonol F docking scores are comparable to rifampicin, with the order of docking score from least favorable to more favorable is sulabiroin-B< sulabiroin-A< rifampicin< broussoflavonol F (-3.397, -3.449, -5.256, -5.961). Molecular dynamics simulations also demonstrated that sulabiroin-B exhibited stable interactions with the target protein, comparable to rifampicin, while sulabiroin-A and broussoflavonol F demonstrated increased fluctuation, suggesting possible instability. Absorption, distribution, metabolism, excretion, and toxicity (ADMET) study verified that all three drugs possess advantageous pharmacokinetic characteristics, with broussoflavonol F exhibiting the most favorable safety and tolerability profile. According to these findings, sulabiroin-B is recognized as the most promising candidate for TB treatment owing to its enhanced stability in molecular dynamics simulations, although broussoflavonol F and sulabiroin-A exhibit intermediate promise. Additional experimental validation is advised to verify their therapeutic

efficacy.

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PMCID: PMC12058314
PMID: 40337249

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56. A snapshot of genomic diversity and transmission clusters of rifampin-resistant Mycobacterium tuberculosis complex in the Central African Republic.

Tuberculosis (Edinb). 2025 May;152:102627. doi: 10.1016/j.tube.2025.102627. Epub 2025 Mar 7.

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Tuberculosis, a significant public health concern in Central African Republic lacks whole-genome-based identification and typing of the Mycobacterium tuberculosis complex strains circulating in populations in that country. Here, we investigated 68 rifampin-resistant clinical isolates collected in 2024 from eight districts in Bangui and surrounding regions. The analysis revealed that all isolates were M. tuberculosis stricto sensu, distributed across nine lineages: L4.1.2.1 Haarlem (n = 20), L4.6 Euro-American (n = 17), L4.6.1.2 Uganda (n = 13), L4.6.2.2 Cameroon (n = 12), and L4.1.1.1 X-Type (n = 2), and single isolates in L4.1 (Euro-American), L4.6.1 (Uganda), L4.3.1 (LAM), and L3

(Delhi-CAS). The antibiotic resistance profile showed that 9/68 (13.2 %) of the M. tuberculosis isolates were susceptible, while 59/68 (86.7 %) exhibited at least one predicted antibiotic resistance. These data provide new insights into tuberculosis transmission in Central African Republic in contrast to reports from neighboring countries, including the absence of Mycobacterium bovis, hence zoonotic tuberculosis and other factors. This preliminary study limited to rifampin-resistant isolates, nevertheless paves the way for a genome-based survey of tuberculosis in Central African Republic which is essential for enhancing the management and control of the deadly tuberculosis that is a public health concern in the country.

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

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

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Drug-resistant tuberculosis (DR-TB) urgently requires safer, more accessible alternatives to bedaquiline (BDQ), which faces critical flaws like cardiotoxicity, high costs, and emerging resistance. WX-081, a promising BDQ alternative, has demonstrated superior anti-TB activity and improved safety in clinical studies. However, its mechanism of action remains unexplored, underscoring the need for further research to optimize its potential in advancing global TB elimination efforts. This study reveals WX-081's dual mechanisms: targeting atpE to disrupt ATP synthase and proton motive force via

resistance screening, gene sequencing, and functional assays while enhancing host immunity through macrophage transcriptomics. Molecular docking confirmed atpE binding sites, and immune activation pathways (NF-κB/MAPK) were identified, positioning WX-081 as a potent, safe anti-DR-TB candidate despite unresolved mechanistic details.IMPORTANCEBedaquiline, a key drug for drug-resistant tuberculosis, is restricted by safety issues impacting its clinical utility. Its next-generation alternative, WX-081, has advanced to Phase III trials but lacks in-depth studies on its mechanism and host immune-modulatory effects, necessitating further research before broad clinical adoption.

DOI: 10.1128/msphere.00149-25
PMID: 40396746

58. Assessing the impact of the TB response in Taiwan - the journey towards ending TB.

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The incidence of TB in Taiwan declined by 62% from 2005 to 2023 (i.e., from 73/100,000 to 28/100,000). Here we review the past two decades of TB epidemiology, policy implementation, and outcomes, identifying gaps and solutions for domestic and global responses. An external review in 2024 assessed National TB Program progress towards the End TB goal, integrating feedback from an International Review Panel and a 2023 expert questionnaire. The findings informed Phase III (2026-2030) of the 'End TB by 2035 Project'. We present review materials, consensus recommendations, and follow-ups through 2024. In 2023, 64% of the TB cases were aged ≥ 65. TB incidence among those < 60 is projected to meet the End TB targets (<10/100,000) by 2035, while elimination (<1 per million) is expected among 0-14-year-olds. During 2005-2024, Taiwan universally adopted new diagnostic tools for drug-resistant TB, shorter regimens

and user-friendly platforms for reporting and case management. Nationwide policy innovations included active case finding, and TB infection (TBI) treatment. Taiwan's consistent investment in TB reflects strong political commitment to End TB. Current challenges include aging, co-morbidities, high TB/TBI among foreign migrant workers and societal disparities, and we suggest that future efforts must leverage artificial intelligence, universal genotyping and greater inter-departmental collaboration.

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PMCID: PMC12068451
PMID: 40365028

59. Diagnostic accuracy of direct drug susceptibility testing of second-line antitubercular drugs.

Microbiol Spectr. 2025 May 6;13(5):e0250624. doi: 10.1128/spectrum.02506-24. Epub 2025 Mar 25.

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It is well-established that direct drug susceptibility testing (DST) of Mycobacterium tuberculosis using a liquid medium for first-line drugs provides accurate and time-saving results. The purpose of this study was to determine whether DST for second-line drugs could be successfully performed using processed smear-positive specimens (direct DST) and whether this method is accurate and may result in a significant reduction in time. The accuracy and shorter turnaround time of this approach were established by comparing the results acquired through direct DST with those obtained through indirect DST. Of the 150 acid-fast bacteria smear-positive sputum specimens that were set up for direct DST, 130 (86.67%) produced results that could be reported. Direct DST reporting took an average of 10 days (range: 9-11 days). The time savings from direct DST to indirect DST, which took into account the time needed to isolate a culture and conduct DST, was 7 days on average (range: 6-9 days). When the direct and indirect DST results were compared, the concordance with levofloxacin (LFX), moxifloxacin (MOX), linezolid (LNZ), and clofazimine (CFZ) were 96.33%, 96.16%, 100%, and 99.24%, respectively. The sensitivity and specificity of the

test result were 93.75%, 83.33%, 100%, and 100%, and 98.0, 99.10, 100, and 99.19% with an accuracy of 98%, 98%, 100%, and 99% for LFX, MOX, LNZ, and CFZ, respectively. Direct DST is a fast and accurate diagnostic technique for detecting second-line drug resistance in tuberculosis.
IMPORTANCE: The significance of this work is that it assesses whether direct drug susceptibility could be used in routine testing to save significant time, which is critical for early diagnosis of resistance and successful treatment.

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PMCID: PMC12053899
PMID: 40130868 [Indexed for MEDLINE]

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

60. Characterisation of M. tuberculosis isolates obtained from Tamil Nadu prevalence survey by whole genome sequencing analysis.

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Recent advances in whole genome sequencing have facilitated the understanding of drug resistance patterns and lineage distribution of M. tuberculosis worldwide. In this study, we aimed to determine the genetic diversity of MTB isolates from presumptive pulmonary TB patients obtained from a state prevalence survey. A total of 124 isolates were available for further characterisation, out of which 71 (57.2 %) and 47 (37.9 %) were subjected to sequencing and phenotypic DST, respectively. The phenotypic resistance profile revealed 3 isolates with multidrug resistance and 3 with mono-INH resistance. Out of 71 isolates, sequencing data were available for 61 (85.9 %), where the lineage distribution and drug resistance profile were analysed in comparison with phenotypic DST results. All the mutations were significant, accounting for one or the other

resistance pattern. The concordance between pDST and gDST for the drugs was above 90 % except for ETH (77 %) and INH (87 %). The phylogenetic analysis of the lineage distribution revealed three clusters with MDR isolates belonging to lineage 1 and lineage 3. While lineage 2 is more frequently associated with MDR distribution both in India and worldwide, we did not find any lineage 2 MDR-TB isolates in our study. The use of WGS analysis improved our understanding of the genetic characteristics of MTB and its correlation with DR-TB transmission.

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PMID: 40354869

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 titled “Characterisation of M. tuberculosis isolates obtained from Tamil Nadu prevalence survey by whole genome sequencing analysis”.

61. Impact of the SARS-COV-2 pandemic on access to health services in Angola: a focus on diagnosis and treatment services for tuberculosis.

Front Public Health. 2025 Apr 24;13:1530782. doi: 10.3389/fpubh.2025.1530782. eCollection 2025.

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INTRODUCTION: The SARS-CoV-2 pandemic had a profound impact on healthcare systems worldwide. In sub-Saharan Africa, it significantly affected several health services for infectious diseases such as HIV; however, less is known

about its impact on Tuberculosis (TB). This study aimed to assess the pandemic's impact on access to health services in Angola, focusing on diagnosis and treatment services for TB.
METHODS: An observational study combining data from routine statistics and surveys based on ad-hoc questionnaires was conducted on TB and non-TB services between 2018 and 2022. On routine data, temporal trends were analyzed comparing different non TB- and TB-specific indicators across the five-year period using the chi-square test. Questionnaires were administered to healthcare professionals from TB/non-TB services and structured interviews were conducted with TB patients to understand their perceptions about the impact of COVID-19 pandemic.
RESULTS: There was a significant decline in access to TB services during the pandemic, with a substantial decrease in reported cases (-15.5% in 2020; -18.3% in 2021) and treatment rate (from 86% in 2019 to 68% in 2020), an increase in multidrug-resistant-TB (from 0.2% in 2018 to 2.1% in 2022) and TB/HIV co-infections (from 6% in 2018 to 8.8% in 2021). The impact was most pronounced in the province of Luanda (capital city). TB services in Angola were disproportionately affected compared to general healthcare access indicators. The healthcare professionals' and patients' questionnaires showed that fear of COVID-19, unavailability of drugs, reduced income, and transportation challenges were the main barriers to healthcare access.
CONCLUSION: The COVID-19 pandemic negatively impacted the TB services provision in Angola. This highlights the urgent need for health systems to develop robust contingency plans to ensure the continuity of TB services during and after public health crises and to maintain essential healthcare services by supporting the healthcare workforce and addressing barriers to patient access.

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PMID: 40342501 [Indexed for MEDLINE]

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

62. Analysis of the impact of crises tuberculosis incidence in Ukraine amid pandemics and war.

Sci Rep. 2025 May 16;15(1):17045. doi: 10.1038/s41598-025-01723-7.

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Ukraine has a historically high burden of tuberculosis (TB). As a result of many years of the healthcare system's reformation, the epidemiological situation has improved. However, under the influence of the COVID-19 pandemic and the illegal invasion by Russia, fluctuations in incidence occur. Through a retrospective, observational analysis using data from the Public Health Center of the Ministry of Health of Ukraine, this study tracked the incidence of TB and multidrug-resistant tuberculosis (MDR TB) and highlights changes caused by crises. The region that maintained a consistently high level of TB and MDR TB throughout the entire study period was Southeastern Ukraine. Data analysis showed a significantly increased TB incidence in Central Ukraine in 2022-2023 (62.75 per 100,000 population) versus 36.55 per 100,000 population in the 2013-2019 period. In Eastern Ukraine, TB incidence decreased markedly (14.95 per 100,000 population) after the beginning of the war in 2022 compared with the pre-COVID-19 pandemic 2013-2019 period (50.36 per 100,000 population). These results indicate a changing pattern of TB incidence throughout Ukraine during the conflict, with lower rates in conflict-affected areas and higher rates in host regions. This reflects the importance of strengthening TB surveillance and control strategies adapted to areas experiencing population influx.

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PMID: 40379776 [Indexed for MEDLINE]

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63.Establishment and evaluation of a naked-eye diagnostic assay for tuberculosis utilizing reverse isothermal amplification-assisted CRISPR-Cas in resource-limited settings.

Drug Target Insights. 2025 May 9;19:31-40. doi: 10.33393/dti.2025.3304.
eCollection 2025 Jan-Dec.

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INTRODUCTION: The current scenario of tuberculosis (TB) caused by Mycobacterium tuberculosis (MTB) has presented an almost insurmountable challenge to hospitals with high patient numbers. Delayed diagnosis of TB is a major hurdle in preventing the employment of efficient therapeutics, leading to the development of drug resistance. Hence, an easily accessible diagnostic method, particularly for resource for resource-limited settings, is pertinent for the rapid identification of MTB-infected patients. In pursuit of developing such an assay, the present study offers a CLAP-TB (CRISPR-Cas coupled RT-LAMP Amplification Protocol for Tuberculosis) assay, which will allow us to diagnose TB rapidly and visually.
METHODS AND RESULTS: Herein, the visual MTB detection consists of a method utilizing 232 different samples (sputum, urine, serum) from 82 patients for reverse transcription loop-mediated isothermal amplification (RT-LAMP). Additionally, the assay also utilizes the integration of a CRISPR-Cas12-based system using different guide RNAs of IS6110 and an internal control POP7 (human RNase P) genes along with visual detection via lateral flow readout-based dipsticks with the unaided eye (~134 min). Overall, the limit of detection for CLAP-TB assay was up to 1 ag of RNA, while the clinical sensitivity and specificity were 98.27% and 100%, respectively, on the pilot scale.
CONCLUSION: Together, our CLAP-TB assay offers proof of concept for a rapid, sensitive, and specific method with the minimum technical expertise required for TB diagnosis in developing and resource-limited settings.

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PMID: 40352342

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

64. Endemic transmission of a Mycobacterium tuberculosis L2.2.M3 sublineage of the L2 lineage within Colon, Panama: A prospective study.

Infect Genet Evol. 2025 Jul;131:105749. doi: 10.1016/j.meegid.2025.105749. Epub 2025 Apr 22.

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Mycobacterium tuberculosis lineage 2 (L2) remains a globally significant lineage associated with increased drug resistance and rapid transmission. The L2 lineage exhibits a hotspot for genetic diversity and evolution in Panama, requiring an in-depth analysis. We conducted a prospective analysis of 274 Mycobacterium tuberculosis L2 isolates from Colon City between January 2021 and October 2023. Drug resistance was determined using GeneXpert and MTBDRplus-Genotype assays, strain lineage was determined by strain-specific PCR (ASO-PCR), and whole-genome sequencing was conducted for phylogenetic analysis. Sequencing data were analyzed using the mtb-call2 pipeline and TB-gen tools to predict drug resistance and sublineage, respectively. Genome-wide single-nucleotide polymorphisms (SNPs) were used for phylogenetic and evolutionary analyses. ASO-PCR results identified all 31.7 % (86/271) isolates as Modern L2.2. WGS analysis of 66 strains confirmed all isolates belonged to the L2.2.1 sublineage. Sixty-four strains were analyzed in depth, with 96.9 % (62/64) classified as pan-susceptible and 3.1 % (2/64) as rifampicin/pyrazinamide-resistant. The sublineage analysis based on SNPs using the TB-gen tool identified a SNP at position 1219683G > A, which genotyped all 64 strains as L2.2.M3 sublineage.

Phylogenetic analysis revealed a correlation with geographical distribution compared to other Latin American L2 isolates. Transmission clusters (≤12 SNPs) were identified and used to determine recent transmission events or TB transmission clusters. These analyses also confirmed a relatively low evolutionary rate within Panama L2 isolates and a highly conserved common ancestor shared with L2 isolates from Peru, Colombia, and Guatemala. These findings suggest endemic transmission of the Mycobacterium tuberculosis L2.2.M3 sublineage in Colon, Panama. We recommend combining genomic information with epidemiological data to accurately track and identify the source hotspot for the L2.2.M3 sublineage and focus control measures.

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

65.Bridging gaps in tuberculosis control: addressing cross-border challenges between India and Pakistan.

J Clin Tuberc Other Mycobact Dis. 2025 Apr 11;39:100526. doi: 10.1016/j.jctube.2025.100526. eCollection 2025 May.

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Tuberculosis (TB) continues to pose a substantial public health concern in South Asia, especially in India and Pakistan, which together represent a considerable portion of the worldwide TB burden. Notwithstanding national initiatives, international cooperation in tuberculosis control is insufficient, presenting a considerable obstacle to disease eradication. This viewpoint underscores the pressing need for improved collaboration between the two nations to tackle common difficulties, such as multidrug-resistant tuberculosis (MDR-TB), inadequate data exchange, and inconsistencies in treatment procedures. We suggest a framework to enhance bilateral tuberculosis control efforts via

enhanced data-sharing methods, standardization of treatment regimens, collaborative research projects, and cross-border healthcare access. The formation of a regional tuberculosis task force and health corridors, equipped with diagnostic and treatment facilities, may improve disease monitoring and patient care, particularly in border areas. Moreover, combined training programs for healthcare professionals and legislative measures might enhance a more synchronized response. The World Health Organization (WHO) advocates for a worldwide plan to eradicate tuberculosis, presenting India and Pakistan with the potential to use international collaborations, like the Worldwide Fund and the Stop TB Partnership, to deploy novel diagnostic methods and therapies. A cohesive approach to tuberculosis enhances regional health security and establishes a benchmark for wider infectious disease management efforts. This viewpoint emphasizes the need for a collaborative strategy for tuberculosis control, promoting policy-oriented initiatives that surpass political divisions to attain a shared objective-diminishing tuberculosis incidence and enhancing public health outcomes in both countries.

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PMID: 40276622

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

66. The effect of pregnancy on the population pharmacokinetics of levofloxacin in South Africans with rifampicin-resistant tuberculosis.

Antimicrob Agents Chemother. 2025 May 7;69(5):e0162624. doi: 10.1128/aac.01626-24. Epub 2025 Apr 1.

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Levofloxacin is a key drug in the prevention and treatment of rifampicin-resistant tuberculosis (RR-TB). There are limited data describing the effect of pregnancy on the pharmacokinetics of levofloxacin. We aimed to characterize the pharmacokinetics of levofloxacin in adults with RR-TB, including the effect of pregnancy. We pooled data from two studies conducted in adult participants treated for RR-TB in South Africa. Treatment regimens in both studies included levofloxacin dosed at 750/1000 mg daily, depending on body weight. We analyzed data from 47 participants, 31 (66%) living with HIV, using nonlinear mixed-effects modeling in NONMEM v7.5.1. Out of 33 female participants, 21 were pregnant, of whom 12 contributed matched antepartum and postpartum pharmacokinetic profiles. Levofloxacin followed one-compartment pharmacokinetics with first-order elimination and absorption with transit absorption compartments. The clearance and volume of distribution for a typical non-pregnant participant (weight: 58 kg; age: 32 years; serum creatinine: 56.2 µmol/L) were 6.06 (95% confidence interval [CI], 5.47 to 6.53) L/h and 85.9 (95% CI, 80.6 to 91.7) L, respectively. Higher serum creatinine levels were associated with lower levofloxacin clearance using a power function with an exponent of -0.367 (95% CI, -0.493 to -0.104). Pregnancy increased levofloxacin clearance by 38.1% (95% CI, 23.4% to 57.1%), with substantially lower exposures in pregnant compared with non-pregnant participants receiving equivalent weight-based doses. To achieve non-pregnant equivalent exposures of levofloxacin, an additional 250 mg tablet may be required, although further study is needed to assess the safety implications of a higher recommended dose in pregnant women.

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PMID: 40167446 [Indexed for MEDLINE]

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

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

Vet Microbiol. 2025 Jun;305:110527. doi: 10.1016/j.vetmic.2025.110527. Epub 2025 Apr 21.

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

interferons (IFNs). These results suggest their potential to orchestrate a robust innate immune response providing valuable insights into the immunological mechanisms underlying the protective effects of these immunostimulants. This underscores their potential role in in vivo studies as vaccine candidates. Furthermore, their ability to enhance antigen recognition via TLR and induce pro-inflammatory cytokines also indicates broader applications in immune modulation, potentially extending protection against heterologous pathogens through trained immunity.

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68.Cost analysis of the TB-PRACTECAL clinical trial on novel tuberculosis treatment regimens.

PLOS Glob Public Health. 2025 Apr 23;5(4):e0003759. doi: 10.1371/journal.pgph.0003759. eCollection 2025.

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Clinical trials are considered to be the largest contributor to pharmaceutical development costs. However, public disclosure of the costs of individual clinical trials is rare. Médecins Sans Frontières (MSF) sponsored a phase 2b-3 randomised controlled trial (TB-PRACTECAL), which identified a new treatment regimen for drug-resistant TB. We aimed to analyse the costs of undertaking a pivotal clinical trial conducted in relatively low-resource health settings and to demonstrate the feasibility of reporting clinical trial costs. TB-PRACTECAL trial costs were analysed using MSF accounting documents. Costs were broken down by cost category, year, and trial site. Total costs for TB-PRACTECAL were €33.9

million and the average cost per patient was €61,460. Twenty-six percent of total costs represented central activities (e.g. trial planning, trial management) and 72% represented trial site activities, with 2% uncategorizable. Within trial site costs, personnel costs were the largest cost (43%) followed by external diagnostic services (11%), medicines (9%), and other medical consumables (7%). Cost variation across trial sites was driven by different varying levels of pre-existing trial infrastructure. A review of previous studies yielded a wide range of cost estimates for clinical trials (ranging US$7-221 million/trial for pharmaceutical phase 2 and 3 trials). Nearly all previous estimates derive from industry reporting that is neither standardized nor auditable; to our knowledge, this is the first published comprehensive analysis of direct expenditures of a specific clinical trial including detailed cost breakdowns. The €34 million cost of TB-PRACTECAL included investments in developing clinical trial infrastructure, the complexity of managing six sites across three health systems, and medical expenditures that are not typical of standard clinical trials. Greater transparency in drug development costs can inform medicine pricing negotiations and is a key element in the design and implementation of more equitable systems of biomedical research and development.

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PMCID: PMC12017904
PMID: 40267985

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69. The Appearance of Osteomyelitis of the Foot and Disseminated Subcutaneous Abscesses During Treatment for Disseminated Tuberculosis Infection in an Immunocompetent Patient: Case Presentation of a Paradoxical Reaction and Literature Review.

Infect Dis Rep. 2025 May 2;17(3):46. doi: 10.3390/idr17030046.

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Background: The appearance of new clinical manifestations (for example, subcutaneous or skin abscesses) during anti-tuberculosis treatment is generally indicative of therapeutic failure. The cause of therapeutic failure may be the presence of a drug-resistant Mycobacterium infection or to the failure to achieve a sufficient concentration of the drugs in the bloodstream. Case report: Here, we report the case of a 25-year-old man suffering from tuberculosis infection with lymph-node and pulmonary involvement and an atypical response to specific therapy. Two weeks after starting four-drug antitubercular treatment, the patient began to experience fever, pain and functional impotence in the left foot and ankle, with subsequent evidence of ankle and tarsal osteomyelitis. Four weeks after starting treatment, the patient presented with several widespread, painful subcutaneous abscesses on the trunk, back and right lower limb. Drainage was performed from the ankle and from one of the abscesses, and polymerase chain reaction (PCR) showed a positive result for M. tuberculosis in both samples, with the absence of resistance to drugs. Anti-tubercular medications were continued, with resolution of the pulmonary and bone involvement but with persistence of subcutaneous abscesses, although subsequent drainages showed the absence of mycobacterium tuberculosis. Conclusions: We describe an unusual presentation of paradoxical reaction in the form of osteomyelitis and subcutaneous abscesses in an immunocompetent TB patient, and we reported other similar cases of paradoxical reactions described in the literature in the last ten years, which demonstrate the importance of considering paradoxical reactions in patients who present with new or worsening signs and symptoms after starting tuberculosis treatment.

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PMCID: PMC12101366
PMID: 40407648

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

70. Evaluation of the cobas MTB and MTB-RIF/INH assay in clinical samples for the detection of Mycobacterium tuberculosis in respiratory specimens.

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The aim of this study was to evaluate the performance of the automated cobas MTB-Real-Time PCR assay for the rapid direct detection of Mycobacterium tuberculosis complex (MTBC) in clinical specimens and the ability of the cobas MTB-RIF/INH assay to correctly detect drug resistance to rifampin (RIF) and isoniazid (INH). The PCR assays were set up on the automated Cobas 6800 system, and the results were compared to liquid culture using BACTEC mycobacteria growth indicator tubes 960 TB system as the gold standard and line probe assays or sequencing results. A total of 500 N-acetyl-L-cysteine/sodium hydroxide (NALC-NaOH)-processed sputum samples were tested with the respective methods. The performance of MTBC detection in pulmonary specimens showed 91.8% sensitivity and 99.3% specificity in comparison to culture. The sensitivity for acid-fast bacteria (AFB) smear-positive specimens and for AFB smear-negative specimens was 100% and 85.1%, respectively. Due to the low prevalence of tuberculosis (TB) resistance in Germany, a collection of resistant TB strains with a wide variety of mutations was analyzed. The cobas MTB-RIF/INH assay detected 19 out of 21 INH-resistant and 22 out of 24 RIF-resistant TB strains. In conclusion, the cobas MTB and the cobas MTB-RIF/INH assays implemented on the automated cobas6800 instrument are reliable and versatile tools for the detection of MTB and RIF/INH resistance.
IMPORTANCE: Our manuscript addresses the WHO recommendation for the use of "moderate-complexity automated NAATs for detection of TB and resistance to rifampicin and isoniazid" as a part of the WHO End TB Strategy. Rapid detection of tuberculosis (TB) patients is essential to preventing TB transmission and finally reducing TB burden. In this study, we present data on the sensitivity and specificity of the novel cobas MTB assay for TB detection in a low-incidence country, demonstrating highly promising results. Additionally, by analyzing TB

strains with various mutations conferring resistance to INH and/or RMP, we assess the opportunities and limitations of the cobas MTB-RIF/INH assay in reliably detecting drug resistance in sputum specimens, thereby facilitating the early onset of appropriate treatment.

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PMID: 40130921 [Indexed for MEDLINE]

Conflict of interest statement: U.E. received speaker honoraria from Roche. All other authors report no conflicts of interest.

71. Vitamin D inhibits apoptosis in THP-1 cells infected with mycobacterium tuberculosis through TNF signaling pathway.

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Vitamin D (VD) has been extensively associated with the resistance against tuberculosis (TB); however, the mechanism underlying the reduction in TB susceptibility by VD remains uncertain. In our prior investigation, we discovered the relationship between VD and mycobacterium tuberculosis M.tb-induced aberrant osteoclastogenesis. Here we report that VD diminishes apoptosis in M.tb-infected THP-1 cells through tumor necrosis factor (TNF) signaling pathway. This novel perspective contributes to the elucidation of the intricate relationship between VD and tuberculosis. In this study, THP-1 cells were infected with the Mycobacterium tuberculosis H37Rv strain (M.tb) for 4h at a MOI of 1 and then treated with 1,25-dihydroxy vitamin D (1,25(OH)2D3) (10-6, 10-8, 10-10M) for 1d respectively. RNA sequencing (RNA-seq) was performed, and differential expression analysis was conducted by the R package edgeR. Immunofluorescence (IF) and immunohistochemistry (IHC) techniques were employed for VDR, TNFR1 and TUNEL in TB patients and serum levels of TNF-α and IL6 were measured simultaneously. Furthermore, the utilization of western blot and

qRT-PCR techniques was employed to investigate the impact of VD on pivotal molecules involved in the TNF signaling pathway. In addition, Bacillus Calmette-Guérin (BCG, ATCC 35734, derived from M.bovis) and VD were administrated by tail vein and articular cavity injection in vivo. Our findings revealed a robust responsiveness of the TNF signaling pathway to M.tb-induced inflammation, resulting in elevated expression of TNF-α, IL-6, and severe apoptosis. VD exhibited significant inhibitory effect on M.tb-induced inflammation and apoptosis both in vitro and in vivo. This study offers novel insights for vitamin D in the study of tuberculous bone destruction.

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72. Contribution of front-line, standard-of-care drugs to bactericidal responses, resistance emergence, and cure in murine models of easy- or hard-to-treat tuberculosis disease.

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By assessing the standard-of-care regimen for tuberculosis (TB) in BALB/c and C3HeB/FeJ mice, we demonstrate that rifampin, with or without pyrazinamide, is essential for an effective bactericidal response and suppression of resistance. Potency measurements in an in vitro lipid-rich model and a rabbit caseum assay recapitulate the significance of rifampin as a sterilizing agent. These outcomes align with clinical performance, thus emphasizing the value of in vitro predictive tools and murine TB models with human-like pathology.

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73.Mycobacterium tuberculosis curli pili reduces oxygen consumption rate of THP-1 macrophages during early infection.

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The development of improved anti-tuberculosis (TB) strategies to address drug-resistance and ineffectual TB treatment regimens should focus on interrupting the initial host-pathogen interaction. This study aimed to elucidate the effect of surface-located adhesin, Mycobacterium tuberculosis (Mtb) curli pili (MTP), on the bioenergetic and metabolomic profiles of THP-1 macrophages during initial stages of infection. Differentiated THP-1 macrophages were infected with wildtype (WT), ∆mtp, or mtp-complemented strains of Mtb. Bioenergetic profiles and metabolic flux were determined and statistical analysis highlighted differences/similarities amongst the THP-1 macrophage groups. The ∆mtp infected THP-1 macrophages mimicked the higher oxygen consumption rate (OCR) for basal respiration, ATP production, maximal respiration and spare respiratory capacity of the uninfected THP-1 macrophages, relative to the WT and mtp-complement infected THP-1 macrophages. The ∆mtp infected THP-1 macrophages displayed the highest compensatory glycolytic rate. Mtb infection caused the redirection of carbon from the tricarboxylic acid cycle to glycolysis, in addition to an increased flux through the pentose phosphate pathway. However, in the ∆mtp infected THP-1 macrophages, the total metabolite abundance was lower, similar to the uninfected THP-1 macrophages. Data indicates that the absence of MTP facilitates prompt clearance of the intracellular pathogen before it establishes a successful infection. This implies that the presence of MTP facilitates the survival of the pathogen during the early stages until infection is established. These findings support the growing evidence that the MTP adhesin is an important virulence factor and interruption of the interaction between pathogen and host, will facilitate swift clearance of the infection by the host.

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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.

74. Vitamin D3 loaded polycaprolactone nanoparticles enhance the expression of the antimicrobial peptide cathelicidin in macrophages.

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Tuberculosis (TB), primarily caused by Mycobacterium tuberculosis, remains a global health burden. Current antibiotic treatments are limited by adverse effects, poor adherence, and drug resistance, necessitating new therapeutic approaches. Recent studies highlight the role of vitamin D3 (VD3) in enhancing host immune responses against the mycobacterium via cathelicidin (an antimicrobial peptide) and autophagy activation. In this study, VD3-loaded poly-ε-caprolactone (PCL) nanoparticles (NPs) were synthesized to enhance cathelicidin expression in macrophages. NPs containing cholecalciferol, calcifediol, and calcitriol were synthesized using an emulsification solvent-evaporation technique. Average sizes of synthesized NPs ranged from 304.7 to 458.7 nm, with polydispersity index (PDI) and zeta potential (ZP) ranging from 0.103 to 0.257 and -17.3 to -7.47 mV, respectively. Encapsulation efficiencies were 9.68%, 10.99%, and 19.28% for cholecalciferol, calcifediol, and calcitriol, respectively. VD3-encapsulated NPs stimulated a dose-dependent increase in cathelicidin expression in THP-1 macrophages. Encapsulated calcifediol and calcitriol (100 ng/ml) induced the expression of 243.46 ng/ml ± 4.55 ng/ml and 396.67 ng/ml ± 25.24 ng/ml of cathelicidin, respectively, which was significantly higher than that induced by the free drugs. These findings suggest that NP encapsulation may offer a more efficient approach to using vitamin D3 for inducing cathelicidin expression as a host-directed treatment for TB.

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75. Whole-genome sequencing analysis to identify antimicrobial resistance regions and virulence factors in Mycobacterium tuberculosis isolates from the Amhara Region, Ethiopia.

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Tuberculosis caused by Mycobacterium tuberculosis complex is a significant global health burden, with drug-resistant TB, especially multidrug-resistant TB, causing severe challenges to treatment. In Ethiopia, a high TB-burden country, drug resistance has continued spreading. However, some studies indicate genetic diversity, transmission dynamics, and resistance-conferring mutations by using targeted amplification, there are limited reports of whole genome sequencing analysis to uncover the antimicrobial resistance and virulent genes. Based on that, the objective of this project was to identify antimicrobial resistance regions and characterize virulence factors in M. tuberculosis isolates through in silico whole-genome sequence analysis. A FASTQ file of 45 M. tuberculosis isolates whole genome sequence was downloaded from the SAR database. Following quality control using FASTQC coupled with MultiQC and trimming with Trimmomatic, de novo assembly was conducted using SPAdes. The Burrows-Wheeler Aligner was used for mapping against the M. tuberculosis H37Rv reference genome, followed by variant calling with FreeBayes. In silico spoligotyping was performed using SpoTyping, and drug resistance mutations were identified with TB-Profiler and validated using Mykrobe. Virulence factors were detected through ABRicate and the Virulence Factor Database. STRING was used to network the virulent genes. All statistical analyses were performed using R software. This study revealed the most prevalent TB-lineage in the Amhara region was L4 (58.53%), followed by

L3 (34.15%), and L1 (4.88%), and in silico spoligotyping classified 90.24% of the isolates into 12 shared types, with SIT 149 (41.46%) and SIT 21 (14.63%) as the most frequent spoligotypes. Seven major genotypic families were identified, with T3-ETH being the dominant family (48.78%). Drug resistance analysis revealed that 38 isolates (92.7%) were multidrug-resistant, and 1 (2.4%) was pre-extensively drug-resistant. Lineage 4 (59%) and its sub-lineage 4.2.2 (51.3%) show the highest resistance. The most frequent mutations to rifampicin, isoniazid, pyrazinamide, ethambutol, streptomycin, ethionamide, fluoroquinolone, and 2nd-line injectable drugs occurred at rpoB Ser450Leu, katG Ser315Thr, pncA c.-11A > G, embB Gly406Ala, rpsL Lys43Arg, Lys88Thr, ethA Met1, gyrA Ala90Val, Asp94Asn, and rrs 1401A > G, respectively. Additionally, a mutation at the mmpR5 gene for bedaquiline and clofazimine resistance occurred in one isolate. A total of 67 virulence genes were identified and 63 of them occurred in all isolates. The high prevalence of MDR-TB and the detection of resistance to both first- and second-line drugs in this study underscore the urgent need for enhanced TB control measures in the Amhara region.

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76. Modulation of immune responses induced by recombinant BCG expressing LTAK63 adjuvant in an immunotherapeutic model vaccine.

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Tuberculosis (TB) remains a major global health issue, with current treatments relying on prolonged multidrug regimens that can reduce patient compliance, and lead to drug resistance. Immunotherapeutic vaccines against Mycobacterium tuberculosis (Mtb) offer a novel approach. We have previously shown that the recombinant BCG expressing LTAK63 adjuvant (rBCG-LTAK63) decreases bacillary load and lung inflammation in Mtb-infected mice. In this work, we further investigated specific immune mechanism induced in mice infected with Mtb and treated with rBCG-LTAK63 in combination with conventional chemotherapy; different routes of administration of rBCG-LTAK63 were evaluated, such as SC, IN, and IV. Immunotherapy with rBCG-LTAK63 induces early innate immune cells migration (predominantly NK cells and monocytes/macrophages) to distinct sites; increased IFN-γ, TNF-α, and IL-17 T cells, FoxP3 expressing regulatory T cells correlating with reduced bacillary load, particularly with IN administration. The findings highlight the potential of rBCG-LTAK63 to complement TB treatment.

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77.Development of a multiplex loop-mediated isothermal amplification (LAMP) method for differential detection of Mycobacterium bovis and Mycobacterium tuberculosis by dipstick DNA chromatography.

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Although human tuberculosis (TB) caused by Mycobacterium bovis is clinically, pathologically, and radiologically indistinguishable from Mycobacterium tuberculosis-caused TB, M. bovis is innately resistant to pyrazinamide, a key first-line drug effective against M. tuberculosis. The rapid differentiation of these two biovars is therefore of high clinical and epidemiologic importance. Most current molecular tools in resource-limited settings identify mycobacteria only to the M. tuberculosis species (MTB) level. In this study, we report a multiplex loop-mediated isothermal amplification (LAMP) method coupled with dipstick chromatography for the rapid and easy differential detection of M. bovis and M. tuberculosis. The assay was optimized and validated using 143 isolates comprising six MTB reference strains, 50 M. bovis isolates, 58 M. tuberculosis isolates, 24 non-tuberculous mycobacterial (NTM) strains, and five

other respiratory pathogens. The multiplex LAMP correctly detected MTB and distinguished between M. tuberculosis and M. bovis simultaneously with sensitivities of 500 fg and 1 pg DNA, respectively, within 60 min, and the results were visualized by dipstick chromatography within 10 min. The assay was specific in that no major respiratory pathogens tested, including NTM strains, were positive. The multiplex dipstick LAMP assay is therefore a useful and accurate low-cost method for the differential identification of M. bovis and M. tuberculosis, especially in endemic areas where bovine and human TB coexist. The distinction between M. bovis and M. tuberculosis can also aid in monitoring the spread of M. bovis to humans and allow for correct treatment, which will ultimately contribute to TB control in both humans and animals.
IMPORTANCE: Human tuberculosis caused by Mycobacterium tuberculosis and Mycobacterium bovis shows similar clinical symptoms; however, the treatment differs because M. bovis is inherently resistant to pyrazinamide, a key first-line drug effective against M. tuberculosis. Most available molecular tools cannot distinguish the two biovars. This study addresses this gap by introducing a multiplex loop-mediated isothermal amplification (LAMP) method coupled with dipstick chromatography that can simultaneously and differentially detect M. bovis and M. tuberculosis within 60 min. The LAMP method does not require sophisticated high-cost equipment and can be easily implemented in resource-limited settings. Our LAMP facilitates rapid and accurate tuberculosis diagnosis, enabling appropriate therapeutic agents to be selected in areas where bovine and human tuberculosis coexist. It can also screen for M. bovis infection in humans and livestock, providing prevalence data in areas where such information is lacking.

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PMID: 40304466

78. Establishing the Exposure-QT Relationship During Bedaquiline Treatment Using a Time-Varying Tuberculosis-Specific Correction Factor (QTcTBT).

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Evaluating QT prolongation induced by anti-tuberculosis (TB) drugs in patients with active TB, who often experience tachycardia, is challenging due to the limitations of Fridericia's correction factor (QTcF) in decorrelating QTc from heart rate (HR). Previous exposure-QTcF analyses in patients with active TB were able to alleviate the limitation of QTcF but required advanced model-based methodologies, incorporating a non-drug-related, "secular" trend in the model to dissociate drug and non-drug-related effects on QT. Recently, we developed and validated a time-varying QT correction method (QTcTBT) that more accurately accounts for the HR changes during TB treatment. In the present work, using data from 429 patients with multidrug-resistant TB across two Phase IIb trials, we re-evaluated the exposure-QTc relationship for bedaquiline by applying QTcTBT instead of QTcF. Our analysis showed that when HR changes were accounted for using QTcTBT, a typical maximum M2 (bedaquiline metabolite) concentration (326 ng/mL, mean maximal concentration (Cmax) at the end of 2-week loading phase) was associated with a 7 ms QTc interval prolongation (90% CI: 5.9-8.2). This estimate closely aligns with the previously reported M2 effect of 7.9 ms (90% CI: 6.8-9.3), derived from the exposure-QTcF model. The consistency between the two methodologies further supports the use of QTcTBT for estimating the QTc prolongation effects of anti-TB drugs.

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PMID: 40369885

79.Development of Carprofen analogues with activity against Mycobacterium tuberculosis.

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Carprofen, a veterinary non-steroidal anti-inflammatory drug, has demonstrated bactericidal activity against Mycobacterium tuberculosis and the closely related model organism M. bovis BCG. Herein, we present the SAR-driven optimisation of three series of carbazole-based carprofen analogues for increased antimycobacterial potency and selectivity over the human monocyte-derived THP-1 cell line. An efficient synthetic route was employed to assemble a range of carprofen analogues which were then evaluated in whole-cell phenotypic assays to establish their activity against well-studied model organisms for M. tuberculosis. The most promising compound was further profiled against M. tuberculosis H37Rv, confirming the identification of a potent antitubercular carbazole with significantly enhanced therapeutic potential.

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80.Morphological, lytic, and genetic characteristics of three Brucella phages isolated from Inner Mongolia Autonomous Region.

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This study comprehensively examined three Brucella phages (A1, NMY-1, and NMY-2) isolated from Inner Mongolia Autonomous Region. Electron microscopy classified them as short-tailed phages. A1 and NMY-1 lysed smooth strains of Brucella abortus, Brucella melitensis, and Brucella suis, while NMY-2 lysed rough strains of Brucella melitensis and Brucella canis. The optimal multiplicity of infection for A1, NMY-1, and NMY-2 was lower than that of TbC. A1 and NMY-2 had short growth cycles, and NMY-1 had a long one. All three phages showed high stability against temperature, pH, and ultraviolet exposure. Their genomes were double-stranded DNA, about 38 kb long with a 48% GC content. For each phage, 53 genes were predicted, with no drug-resistance, virulence, or lysogenic genes identified. SNP and InDel analysis revealed significant differences in genes encoding hypothesized tail-collar proteins. Based on SNP data, the phylogenetic tree indicated that phage BkW (GenBank: KC556893) was the closest relative of A1, NMY-1, and NMY-2. These findings significantly enhance our understanding of Brucella phage diversity, which is crucial for developing phage-based biocontrol strategies. The host-lysis spectra can guide the selection of effective phages for treating Brucella infections. The absence of harmful genes makes these phages potential safe candidates for phage therapy. Moreover, the genetic and phylogenetic insights support further research on phage evolution and classification.

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81. Post-market quality assessment of antibiotics: findings from a cross-sectional study using standardised patients in Tabalong and Bekasi districts, Indonesia.

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OBJECTIVES: In Indonesia, antibiotics are often purchased without a prescription at community pharmacies, contrary to current regulations. This practice may increase the risk of out-of-specification (OOS) medicines being dispensed, potentially contributing to treatment failure and antibiotic resistance. To address this concern, we assessed the quality of antibiotics purchased without a prescription at private drug retail outlets (PDROs) in Indonesia.
DESIGN AND SETTING: We conducted a cross-sectional study in Tabalong and Bekasi, Indonesia, using standardised patients (SPs) who purchased antibiotics without a prescription for three clinical scenarios: upper respiratory tract infection (URTI), tuberculosis (TB) and child diarrhoea. The pharmacies and drug stores were randomly selected from each subdistrict based on the probability proportional method. We measured the active pharmaceutical ingredient (API) content of the antibiotic samples using high-performance liquid chromatography (HPLC).
SAMPLES AND ANALYSIS: The quality of 183 antibiotics including amoxicillin tablets (148/183, 80.9%, 95% CI 74.7% to 86.1%), amoxicillin dry syrup (12/183, 6.6%, 95% CI 3.6% to 10.8%), ampicillin tablets (5/183, 2.7%, 95% CI 1.1% to 5.9%) and ciprofloxacin tablets (18/183, 9.8%, 95% CI 6.2% to 14.8%) obtained from 117/166 (70.5%, 95% CI 62.8 to 77.2) PDROs were tested. Descriptive statistics were used to describe the characteristics of the purchased antibiotics, and the API content of each antibiotic was compared against the United States Pharmacopeia 43-National Formulary 38 (USP 43-NF 38) standards in absolute values and percentages.
RESULTS: Almost all samples produced in Indonesia (182/183, 99.5%, 95% CI 97.5% to 99.9%) were unbranded (123/183, 67.2%, 95% CI 60.2% to 73.7%) or branded generic (60/183, 32.8%, 95% CI 26.3% to 39.8%) and packaged in strips (165/183, 90.2%, 95% CI 85.2% to 93.8%). Around 12/183 (6.6%, 95% CI 3.6% to 10.8%) antibiotics were found to be OOS; these were mostly amoxicillin 125 mg dry syrup (6/12, 50%, 95% CI 24.3% to 75.7%) and ciprofloxacin 500 mg tablet (5/18, 27.8%, 95% CI 11.5% to 50.6%). Around 33% (4/12, 95% CI 12.5% to 61.2%) of amoxicillin 125 mg dry syrup samples had an API content above the label claim, the highest being 187%, whereas 16.7% (2/12, 95% CI 3.6% to 43.6%) were below the label claim, the lowest being 64%. About 27.8% (5/18, 95% CI 11.5% to 50.6%) of ciprofloxacin samples tested had an API content above the label claim; the highest was 120%.
CONCLUSION: While the proportion of OOS antibiotics identified was relatively small, at a population level, it represents a significant proportion of sub-optimally treated infections.

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Conflict of interest statement: Competing interests: None declared.

82. Resistance to tuberculin skin test/interferon-gamma release assay conversion among highly TB exposed, HIV infected goldminers in South Africa.

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BACKGROUND: A small proportion of goldminers in South Africa resist tuberculin skin test (TST)/interferon-gamma release assay (IGRA) conversion despite high rates of HIV and prolonged exposure to TB. We conducted a study among HIV-infected goldminers to determine the: i) proportion who resisted TST/IGRA conversion and ii) epidemiological factors associated with resistance to TST/IGRA conversion.
METHODS: We enrolled HIV-infected goldminers who were on antiretroviral treatment, aged 33-60 years, with ≥15 years' service, no prior or current TB, no silicosis, and with body mass index >18.5 kg/m2. TST/IGRA conversion was assessed at baseline, 6 months, and 12 months using TST and QuantiFERON-TB-Gold-Plus (QFT-Plus). Miners were considered resisters if they had a zero TST response and a negative QFT-Plus at all visits. Logistic regression was used to identify epidemiological factors associated with TST/IGRA conversion resistance.
RESULTS: We enrolled 245 HIV-infected miners with median age of 48 years

(interquartile-range [IQR]: 44-52 years) and median CD4 count, 506 cells/ μ L (IQR: 372-677 cells/ μ L). Overall, 98.4% (241) were males and 99.2% (243) were Black/African with a median time of 24 years (IQR: 18-29 years) in the workforce. Of those completing all follow-ups, 24.3% (50/206) resisted TST/IGRA conversion. Miners who had a history of taking isoniazid preventive therapy (IPT) (adjusted odds ratio (aOR) 2.34; 95% confidence interval (CI): 1.14-4.80; p = 0.020) were more likely to resist TST/IGRA conversion. However, those from Mozambique (aOR 0.16; 95% CI: 0.04-0.71; p = 0.016) and those who had a CD4 count ≥500 cells/ μ L (aOR 0.46; 95% CI: 0.23-0.92; p = 0.028) were less likely to resist TST/IGRA conversion.
CONCLUSION: Similar to previous longitudinal cohort studies, we found a small proportion of HIV-infected goldminers who resisted TST/IGRA conversion. This was positively associated with prior IPT, but negatively associated with lower CD4 count and being from Mozambique. However, mechanisms underlying TST/IGRA conversion resistance are not well understood.

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

83. Discovery of natural CdnP inhibitors through structure-based virtual screening and molecular dynamics simulations.

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Tuberculosis, caused by Mycobacterium tuberculosis, remains one of the most lethal infectious diseases both historically and in the post-coronavirus disease 2019 era. CdnP (Rv2837c) functions as a bifunctional oligoribonuclease and 3'(2')-phosphoadenosine 5'-phosphate-phosphatase that impedes host immune responses by recognizing bacterial cyclic dinucleotides such as c-di-AMP, which serve as pathogen-associated molecular patterns. Despite its significance, strategies targeting CdnP remain limited. Through high-throughput virtual screening and enzymatic assays, we identified four natural product inhibitors: one coumarin derivative (macrosporusone A) and three flavonoid glucosides (ligustroflavone, rhoifolin, and neodiosmin). Surface plasmon resonance measurements confirmed direct binding of these compounds to CdnP with nanomolar to micromolar affinities. Molecular dynamics simulations elucidated a dual inhibitory mechanism wherein these compounds competitively occupy the product (AMP)-binding site while simultaneously constraining conformational plasticity of the substrate-binding domain. Evolutionary analysis demonstrated that these inhibitors exhibit broad-spectrum activity against bacterial CdnP orthologs while showing minimal inhibition of host-derived 2',3'-cGAMP-specific phosphodiesterases, suggesting favorable selectivity. Notably, ligustroflavone exhibited superior inhibitory potency. In contrast, FDA-approved phosphodiesterase inhibitors showed poor activity against bacterial orthologs. These findings provide a foundation for developing novel host-directed therapeutics against tuberculosis that could potentially enhance stimulator of interferon genes (STING)-mediated immune responses without exerting selective pressure for antimicrobial resistance.
IMPORTANCE: Tuberculosis (TB) remains a leading cause of mortality worldwide, with drug resistance posing a significant challenge to global control efforts. This study represents a major contribution to the field by identifying novel natural product inhibitors targeting CdnP (Rv2837c), a c-di-AMP-specific phosphodiesterase critical for Mycobacterium tuberculosis pathogenesis. The significance of this work lies in its innovative approach to TB therapy by perturbing bacterial nucleotide signaling pathways rather than directly inhibiting bacterial growth. By selectively targeting bacterial CdnP while avoiding host phosphodiesterases, these compounds-particularly ligustroflavone and other flavonoid glucosides-offer a promising foundation for developing host-directed therapeutics with potentially reduced selective pressure for antimicrobial resistance. Furthermore, the detailed structural insights and inhibitory mechanisms elucidated through molecular dynamics simulations provide valuable knowledge for rational drug design. This research bridges natural product discovery with computational biology to address the urgent need for novel TB treatments, especially against drug-resistant strains, presenting a significant advancement toward more effective therapeutic interventions for this persistent global health threat.

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PMID: 40304517

84.Inhibitory effect of carvedilol on bedaquiline metabolism in vitro and in vivo.

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Bedaquiline has recently been approved for the treatment of multidrug-resistant tuberculosis. Carvedilol is a cardiovascular medication extensively used in the treatment of heart failure and hypertension. In this study, Sprague-Dawley rats, rat liver microsomes (RLM), human liver microsomes (HLM), and recombinant human CYP3A4 were used to explore the effect of carvedilol on the metabolism of bedaquiline. Ultra-performance liquid chromatography-tandem mass spectrometry was used to facilitate the quantification of the analyte concentrations. In vitro, carvedilol did not exhibit time-dependent inhibition of bedaquiline, which aligns with the half-maximal inhibitory concentration (IC50) shift results. The IC50 values of carvedilol were 15.35 ± 0.43 μM in RLM, 7.55 ± 0.74 μM in HLM, and 0.79 ± 0.05 μM in CYP3A4. Besides, the inhibition type of carvedilol was found to be mixed, un-competitive, and mixed in RLM, HLM, and CYP3A4, respectively. In vivo, the co-administration of carvedilol with bedaquiline resulted in a significant increase in the area under the plasma concentration-time curve (AUC)(0 - t), AUC(0 - ∞), and Cmax of bedaquiline while decreasing its CLz/F. Lay summary: Carvedilol could inhibit the metabolism of bedaquiline in vitro and in vivo, with different mechanisms in different enzymatic reaction systems. Hence, caution should be exercised when combining bedaquiline with carvedilol.

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

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

85. The Prognostic Value of the Prostate Adenocarcinoma With Ductal Feature in Patients With Advanced Prostate Cancer Treated With Abiraterone Acetate.

Prostate. 2025 May;85(7):659-669. doi: 10.1002/pros.24869. Epub 2025 Mar 4.

Shi Y(1), Wei X(1), Zhao F(1), Chen J(1), Sun G(1), Zhang X(1), Liang J(1), Hu X(1), Shen P(1), Liu Z(1), Nie L(2), Chen N(2), Zhao J(1), Zeng H(1).

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BACKGROUND: The prognostic value of the prostate adenocarcinoma (PAC) with ductal feature in patients with advanced prostate cancer treated with abiraterone acetate has not been scrutinized. This study aims to explore the predictive value of PAC with ductal feature on the therapeutic efficacy of abiraterone therapy in metastatic prostate cancer (mPCa) patients.
METHODS: We retrospectively analyzed data from 569 patients with mPCa receiving abiraterone at either the metastatic hormone-sensitive (mHSPC, N = 165) or castration-resistant prostate cancer (mCRPC, N = 404) stage. PSM was performed to balance the baseline characteristics between individuals with and without ductal features. Kaplan-Meier curves and Cox regression were used to analyze the predictive significance of ductal feature on abiraterone efficacy, including PSA response, PSA progression-free survival (PSA-PFS), radiographic progression-free survival (rPFS), and overall survival (OS).
RESULTS: Totally, ductal feature was detected in 40/569 (7.0%) men, with 18 and 22 in the mHSPC and mCRPC cohorts, respectively. The PSA response rate was comparable for people with and without ductal features for both cohorts. Notably, in the mHSPC cohort, patients with and without ductal features shared similar median PSA-PFS (not reached vs. 32.6-months, p = 0.593) and rPFS (not reached vs. 35.0-months, p = 0.768). Similar results were observed in the mCRPC cohort (median PSA-PFS: 21.2- vs. 11.6-months, p = 0.100; median rPFS: 34.6- vs. 18.7-months, p = 0.092). COX regression further revealed that ductal feature was not an indicator of unfavorable PSA-PFS or rPFS in the mHSPC and mCRPC cohort.
CONCLUSION: In conclusion, our findings indicated that there is insufficient evidence to differentiate the therapeutic efficacy of AA in mPCa based on the presence or absence of ductal features. However, further validation through

larger-scale studies is required to substantiate them.

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PMID: 40035401 [Indexed for MEDLINE]

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

86. Antibiotic susceptibility patterns of bacterial uropathogens at a private tertiary hospital in Uganda: a retrospective study.

BMC Infect Dis. 2025 Apr 25;25(1):605. doi: 10.1186/s12879-025-11005-2.

Nakandi RM(1)(2), Kakeeto P(3), Kihumuro RB(4)(5), Kanyike AM(6)(4)(5), Nalunkuma R(6)(4), Lugwana RS(3), Kasozi F(3), Muyanja D(7), Mayega NR(8), Mutesasira JK(8), Mutebi RK(6), Patricia K(9), Nasozi R(10), Namulema E(11), Ssebuufu R(4).

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BACKGROUND: Urinary tract infections are disproportionately prevalent in low- and middle-income countries, where a significant portion of the population relies on over the counter and self-prescriptions to manage symptoms. This practice has contributed to a concerning shift in antimicrobial resistance trends, among the most recommended treatments.
METHODS: A cross-sectional retrospective study was conducted at Mengo Hospital's medical laboratory, utilizing data from the hospital management system between

January 2019 and July 2023. A total of 1,091 urine samples were collected and cultured on Cysteine Lactose Electrolyte Deficient agar. Of the samples analyzed, 476 showed significant bacteria growth (> 105 colony-forming units). Organisms were identified using Gram staining and other biochemical techniques. Antibiotic susceptibility testing was performed using the Kirby-Bauer disc diffusion method. Data was entered into Microsoft Excel, cleaned, and analyzed using STATA 15.0.
RESULTS: Among the 476 records with bacterial growth, 74.8% were females. The highest incidence of infection occurred in individuals aged 50 years and above (31.7%). The most isolated bacterial organisms were Gram-negative Escherichia coli (39.5%) and Gram-positive Staphylococcus aureus (25.6%). E.coli was most isolated among females (78.2%, $p < 0.0001$). Imipenem (83.9%), amikacin (72%), and nitrofurantoin (65.5%) were the antimicrobial agents to which isolated bacteria exhibited the highest sensitivity. Conversely, bacteria showed highest resistance to ciprofloxacin and ofloxacin of 65.5% and 64.5%, respectively.
CONCLUSIONS: The increasing resistance of uropathogens to commonly prescribed and affordable antibiotics is a growing concern. Ciprofloxacin, a widely used empirical treatment, has shown a significant shift towards resistance, highlighting the need for healthcare facilities to utilize bacteriology laboratories for culture and antimicrobial susceptibility testing, and surveillance to inform standard treatment guidelines.

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PMID: 40281488 [Indexed for MEDLINE]

Conflict of interest statement: Declarations. Competing interests: The authors declare no competing interests. Conflict of interest: The authors declare no conflicting interests. Ethical approval: The ethical principles of involvement of human research subjects as outlined in the Nuremberg Code and Declaration of Helsinki were strictly adhered to for this study. Ethical approval was obtained from the Mengo Hospital research and ethics committee under approval number MH-2023-27. Additional approval was obtained from the data manager to access patients' records from the hospital health management information system. A waiver of consent was written and approved for the use of patient information for the study by the ethics committee of the hospital. Patients' records were reviewed, and confidentiality was maintained. Clinical trial number: not applicable. Clinical trial number: Not applicable.

87. Prioritization of novel anti-infective stilbene derivatives by combining metabolomic data organization and a stringent 3R-infection model in a knowledge

Graph.

RSC Adv. 2025 Apr 23;15(17):13010-13030. doi: 10.1039/d4ra08421g. eCollection 2025 Apr 22.

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The rising threat of multidrug-resistant tuberculosis, caused by Mycobacterium tuberculosis, underscores the urgent need for new therapeutic solutions to tackle the challenge of antibiotic resistance. The current study utilized an innovative 3R infection model featuring the amoeba Dictyostelium discoideum infected with Mycobacterium marinum, serving as stand-ins for macrophages and M. tuberculosis, respectively. This high-throughput phenotypic assay allowed for the evaluation of more specific anti-infective activities that may be less prone to resistance mechanisms. To discover novel anti-infective compounds, a diverse collection of 1600 plant NEs from the Pierre Fabre Library was screened using the latter assay. Concurrently, these NEs underwent untargeted UHPLC-HRMS/MS analysis. The biological screening flagged the NE from Stauntonia brunoniana as one of the anti-infective hit NEs. High-resolution HPLC micro-fractionation coupled with bioactivity profiling was employed to highlight the natural products driving this bioactivity. Stilbenes were eventually identified as the primary active compounds in the bioactive fractions. A knowledge graph was then used to leverage the heterogeneous data integrated into it to make a rational selection of stilbene-rich NEs. Using both CANOPUS chemical classes and Jaccard similarity indices to compare features within the metabolome of the 1600 plant NEs collection, 14 NEs rich in stilbenes were retrieved. Among those, the roots of Gnetum edule were flagged as possessing broader chemo-diversity in their stilbene content, along with the corresponding NE also being a strict anti-infective. Eventually, a total of 11 stilbene oligomers were isolated from G. edule and fully characterized by NMR with their absolute stereochemistry

established through electronic circular dichroism. Six of these compounds are new since they possess a stereochemistry which was never described in the literature to the best of our knowledge. All of them were assessed for their anti-infective activity and (-)-gnetuhainin M was reported as having the highest anti-infective activity with an IC50 of 22.22 μM.

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PMCID: PMC12015462
PMID: 40271414

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

88. Solid-phase synthesis of aryl squaramides using Liebeskind-Srogl cross-coupling.

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We present a method for the synthesis of aryl-substituted squaramides through the Liebeskind-Srogl cross-coupling reaction performed on solid support. This approach offers a unique application for the cross-coupling reaction, allowing for the rapid and efficient production of a diverse range of substituted analogs within a combinatorial framework. Through our technique, we successfully synthesized derivatives that were previously unattainable. Additionally, the optimized conditions have been effectively applied in a scale-up reaction. The derivatives show potential for the treatment of drug-resistant tuberculosis.

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PMCID: PMC12047450
PMID: 40322251

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to influence the work reported in this paper.

89. Estimating the Incidence of Antimicrobial-Resistant Neisseria gonorrhoeae in the United States Among Men and Women Aged 15 to 39 Years, 2008 to 2019.

Sex Transm Dis. 2025 May 1;52(5):273-278. doi: 10.1097/OLQ.0000000000002128. Epub 2024 Dec 24.

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BACKGROUND: The Gonococcal Isolate Surveillance Project (GISP) was established to monitor antimicrobial resistance (AR) in Neisseria gonorrhoeae in the United States. Isolates collected in GISP undergo antimicrobial susceptibility testing allowing for estimates of resistance, based on exceeding minimum inhibitory concentrations (MICs), to be calculated.
METHODS: We estimated the annual number and proportion of gonococcal infections with antibiotic resistance or elevated MICs (AR/eMICs) against 6 antibiotics for men and women aged 15 to 39 years in the United States using male urethral specimens collected in GISP during 2008-2019. Although GISP only measured MICs for male gonococcal infections, this study estimated AR/eMICs in women using data from men with female sex partners. GISP data were weighted against national gonorrhea case report data based on 4 variables (age group, year of report, US Census region, and race/Hispanic ethnicity) to estimate annual, national proportions of gonococcal infections with AR/eMICs. These weighted proportions were then multiplied by national estimates of incident gonococcal infections to calculate the number of incident gonococcal infections with AR/eMICs nationally.
RESULTS: Women had a higher estimated number of cases with AR/eMICs compared with men (440,900 vs. 387,200 in 2019), although the estimated percentage of gonococcal infections with AR/eMICs was lower in women (50.7% vs. 54.4% in 2019). Elevated MICs to ceftriaxone remained below 1% throughout the study period.
CONCLUSIONS: Our analysis indicates that there are more women with AR/eMICs gonorrhea than men. Although the proportion of cases that are resistant to any one antimicrobial is increasing, eMICs to ceftriaxone remains low.

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Conflict of interest statement: Conflict of Interest and Sources of Funding:
None declared.

Recent TB News

1. **$15.3 Million Unitaid Investment to Strengthen Community-Led Action on Drug-Resistant TB in 16 Countries**

https://www.stoptb.org/news/153-million-unitaid-investment-strengthen-community-led-action-drug-resistant-tb-16-countries

With support from Unitaid, the Stop TB Partnership will now lead the new RESPECT (Reshaping People-Centric Empowered Community-led DR-TB Treatment) project in 16 countries, with the goal of empowering TB-affected communities and strengthening community-led action and initiatives on drug-resistant TB (DR-TB).