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1. Drug-Resistant Tuberculosis Case-Finding Strategies: Scoping Review.

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BACKGROUND: Finding individuals with drug-resistant tuberculosis (DR-TB) is important to control the pandemic and improve patient clinical outcomes. To our knowledge, systematic reviews assessing the effectiveness, cost-effectiveness, acceptability, and feasibility of different DR-TB case-finding strategies to inform research, policy, and practice, have not been conducted and the scope of primary research is unknown.
OBJECTIVE: We therefore assessed the available literature on DR-TB case-finding strategies.
METHODS: We looked at systematic reviews, trials, qualitative studies, diagnostic test accuracy studies, and other primary research that sought to improve DR-TB case detection specifically. We excluded studies that included patients seeking care for tuberculosis (TB) symptoms, patients already diagnosed

with TB, or were laboratory-based. We searched the academic databases of MEDLINE, Embase, The Cochrane Library, Africa-Wide Information, CINAHL (Cumulated Index to Nursing and Allied Health Literature), Epistemonikos, and PROSPERO (The International Prospective Register of Systematic Reviews) using no language or date restrictions. We screened titles, abstracts, and full-text articles in duplicate. Data extraction and analyses were carried out in Excel (Microsoft Corp).
RESULTS: We screened 3646 titles and abstracts and 236 full-text articles. We identified 6 systematic reviews and 61 primary studies. Five reviews described the yield of contact investigation and focused on household contacts, airline contacts, comparison between drug-susceptible tuberculosis and DR-TB contacts, and concordance of DR-TB profiles between index cases and contacts. One review compared universal versus selective drug resistance testing. Primary studies described (1) 34 contact investigations, (2) 17 outbreak investigations, (3) 3 airline contact investigations, (4) 5 epidemiological analyses, (5) 1 public-private partnership program, and (6) an e-registry program. Primary studies were all descriptive and included cross-sectional and retrospective reviews of program data. No trials were identified. Data extraction from contact investigations was difficult due to incomplete reporting of relevant information.
CONCLUSIONS: Existing descriptive reviews can be updated, but there is a dearth of knowledge on the effectiveness, cost-effectiveness, acceptability, and feasibility of DR-TB case-finding strategies to inform policy and practice. There is also a need for standardization of terminology, design, and reporting of DR-TB case-finding studies.

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2. Mycobacterium tuberculosis Biofilms: Immune Responses, Role in TB Pathology, and Potential Treatment.

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Tuberculosis (TB) is a major public health problem worldwide, and the burden of drug-resistant TB is rapidly increasing. Although there are literatures about the Mtb biofilms, their impact on immune responses has not yet been summarized. This review article provides recent knowledge on Mycobacterium tuberculosis (Mtb) biofilm-immunity interactions, their importance in pulmonary TB pathology, and immune-based therapy targeting Mtb biofilms. Pellicle/biofilm formation in Mtb contributes to drug resistance, persistence, chronicity, surface attachment, transfer of resistance genes, and modulation of the immune response, including reduced complement activation, changes in the expression of antigenic proteins, enhanced activation of T-lymphocytes, elevated local IFNγ+ T cells, and strong antibody production. The combination of anti-TB drugs and anti-biofilm agents has recently become an effective strategy to improve TB treatment. Additionally, immune-targeted therapy and biofilm-based vaccines are crucial for TB prevention.

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3. Application of metagenomic next-generation sequencing for rapid molecular identification in spinal infection diagnosis.

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OBJECTIVE: This study aimed to determine the sensitivity and specificity of metagenomic next-generation sequencing (mNGS) for detecting pathogens in spinal infections and to identify the differences in the diagnostic performance between mNGS and targeted next-generation sequencing (tNGS).
METHODS: A total of 76 consecutive patients with suspected spinal infections who underwent mNGS, culture, and histopathological examinations were retrospectively studied. The final diagnosis of the patient was determined by combining the clinical treatment results, pathological examinations, imaging changes and laboratory indicators. The sensitivity and specificity of mNGS and culture were determined.
RESULTS: The difference between the two detection rates was statistically significant ($p < 0.001$), with mNGS exhibiting a significantly higher detection rate (77.6% versus 18.4%). The average diagnosis time of mNGS was significantly shorter than that of bacterial culture ($p < 0.001$, 1.65 versus 3.07 days). The sensitivity and accuracy of mNGS were significantly higher than that of the culture group ($p < 0.001$, 82.3% versus 17.5%; 75% versus 27.6%), whereas the specificity of mNGS (42.9%) was lower than that of the culture group ($p > 0.05$, 42.9% versus 76.9%). The sensitivity, specificity, accuracy, and positive predictive value (PPV) of pus were higher than those of tissue samples for mNGS, whereas for culture, the sensitivity, specificity, accuracy, and PPV of tissue samples were higher than those of pus. tNGS demonstrated higher sensitivity and accuracy in diagnosing tuberculosis (TB) than mNGS (80% versus 50%; 87.5% versus 68.8%).
CONCLUSION: mNGS for spinal infection demonstrated better diagnostic value in developing an antibiotic regimen earlier, and it is recommended to prioritize pus samples for testing through mNGS. Moreover, tNGS outperformed other methods for diagnosing spinal TB and identifying antibiotic-resistance genes in drug-resistant TB.

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Conflict of interest statement: Author ZS was employed by the company Dinfectome Inc. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be constructed as a potential conflict of interest.

4. Candidate anti-tuberculosis medicines and regimens under clinical evaluation.

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BACKGROUND: Tuberculosis (TB) is the leading cause of mortality by an infectious disease worldwide. Despite national and international efforts, the world is not on track to end TB by 2030. Antibiotic treatment of TB is longer than for most infectious diseases and is complicated by frequent adverse events. To counter emerging Mycobacterium tuberculosis drug resistance and provide effective, safe drug treatments of shorter duration, novel anti-TB medicines, and treatment regimens are needed. Through a joint global effort, more candidate medicines are in the clinical phases of drug development than ever before.
OBJECTIVES: To review anti-TB medicines and treatment regimens under clinical evaluation for the future treatment of drug-susceptible and drug-resistant TB.
SOURCES: Pre-clinical and clinical studies on novel anti-TB drugs.
CONTENT: Description of novel protein synthesis inhibitors (oxazolidinones and oxaboroles), respiratory chain inhibitors (diarylquinolines and cytochrome bc1 complex inhibitor), cell wall inhibitors (decaprenylphosphoryl-β-d-ribose 2'-epimerase, inhibitors, thioamides, and carbapenems), and cholesterol metabolism inhibitor currently evaluated in clinical trials and novel clinical

trial platforms for the evaluation of treatment regimens, rather than single entities.
IMPLICATIONS: A large number of potential anti-TB candidate medicines and innovations in clinical trial design for the evaluation of regimens, rather than single medicines, provide hope for improvements in the treatment of TB.

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PMID: 38909687

5. Timing and predictors of death during treatment in patients with multidrug/rifampin-resistant tuberculosis in South Korea.

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BACKGROUND/AIMS: This study aimed to investigate the timing and predictors of death during treatment among patients with multidrug/rifampin-resistant tuberculosis (MDR/RR-TB) in South Korea.
METHODS: This was a retrospective cohort study that included MDR/RR-TB cases notified between 2011 and 2017 in South Korea.
RESULTS: Among 7,226 MDR/RR-TB cases, 699 (9.7%) died at a median of 167 days (IQR 51-358 d) from the initiation of MDR-TB treatment. The cumulative proportion of all-cause death was 35.5% at 90 days and 52.8% at 180 days from treatment initiation. TB-related deaths occurred at a median of 133 days (IQR 32-366 d), which was significantly earlier than the median of 184 days (IQR 68-356 d) for non-TB-related deaths ($p = 0.002$). In a multivariate analysis, older age was the factor most strongly associated with death, with those aged ≥ 75 years being 68 times more likely to die (aHR 68.11, 95% CI 21.75-213.26), compared those aged ≤ 24 years. In addition, male sex, comorbidities (cancer,

human immunodeficiency virus, and end stage renal disease), the lowest household income class, and TB-specific factors (previous history of TB treatment, smear positivity, and fluoroquinolone resistance) were identified as independent predictors of all-cause death.
CONCLUSION: This nationwide study highlights increased deaths during the intensive phase and identifies high-risk groups including older people and those with comorbidities or socioeconomic vulnerabilities. An integrated and comprehensive strategy is required to reduce mortality in patients with MDR/RR-TB, particularly focusing on the early stages of treatment and target populations.

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6. Beyond the diagnosis of drug-resistant Tuberculosis in Norway: patients' experiences before, during and after treatment.

BMC Public Health. 2024 Jul 6;24(1):1801. doi: 10.1186/s12889-024-19342-8.

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BACKGROUND: This study aims to explore the varied experiences of patients with

drug-resistant tuberculosis in Norway. The study emphasizes challenges and implications of being diagnosed with drug-resistant tuberculosis, including the impact on psychosocial health during the diagnosis, disease, treatment, isolation and recovery phases. Norway is a low endemic country of tuberculosis. Most patients are immigrants, and some of them have recently arrived in the country. Patients undergoing treatment for drug-resistant tuberculosis endure prolonged and demanding treatment that could affect their psychosocial health.
METHODS: This qualitative study conducted 16 in-depth interviews with individuals aged 18 years and above who were diagnosed with drug-resistant tuberculosis. All participants completed the treatment between 2008 and 2020. Fourteen participants were immigrants, and eight of them had resided in Norway for less than four years before diagnosis. Data analysis followed the six-phase reflexive thematic analysis framework, focusing on identifying patterns in participants' experiences, thoughts, expectations and attitudes.
RESULTS: The narratives of the participants highlighted the complexities of navigating the diagnosis of drug-resistant tuberculosis, treatment, side effects and life after treatment. Immigrants encountered additional challenges, including language barriers and adapting to new social environments. All participants reported experiencing physical health issues that additionally affected their mental health and social activity. Several participants had a delayed or prolonged diagnosis that complicated their disease trajectory. Participants with suspected or confirmed contagious pulmonary tuberculosis underwent hospital isolation for periods ranging from weeks to six months. The participants reported mental health issues, social isolation and stigma, however few were offered follow-up by a psychologist. Many participants had persistent problems at the time of the interviews. Three main themes emerged from the analysis: Delayed and prolonged diagnosis; Psychosocial impact of isolation during treatment; The life after tuberculosis.
CONCLUSION: This study highlights the enduring impact of drug-resistant tuberculosis on patients and the significance of timely diagnosis, psychosocial support and post-treatment follow-up. The participants universally faced serious implications of the disease, including stigma and isolation. Participants who experienced delayed diagnosis, reflected on missed early intervention opportunities. We recommend further research in low endemic countries to evaluate the international and local recommendations on psychosocial support.

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7. A Transcriptomic Biomarker Predicting Linezolid-Associated Neuropathy During Treatment of Drug-Resistant Tuberculosis.

Pathog Immun. 2024 Jun 25;9(2):25-42. doi: 10.20411/pai.v9i2.705. eCollection 2024.

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BACKGROUND: Neuropathic adverse events occur frequently in linezolid-containing regimens, some of which remain irreversible after drug discontinuation.
OBJECTIVE: We aimed to identify and validate a host RNA-based biomarker that can predict linezolid-associated neuropathy before multidrug-resistant/rifampicin-resistant tuberculosis (MDR/RR-TB) treatment initiation and to identify genes and pathways that are associated with linezolid-associated neuropathy.
METHODS: Adult patients initiating MDR/RR-TB treatment including linezolid were

prospectively enrolled in 3 independent cohorts in Germany. Clinical data and whole blood RNA for transcriptomic analysis were collected. The primary outcome was linezolid-associated optic and/or peripheral neuropathy. A random forest algorithm was used for biomarker identification. The biomarker was validated in an additional fourth cohort of patients with MDR/RR-TB from Romania. RESULTS: A total of 52 patients from the 3 identification cohorts received linezolid treatment. Of those, 24 (46.2%) developed peripheral and/or optic neuropathies during linezolid treatment. The majority (59.3%) of the episodes were of moderate (grade 2) severity. In total, the expression of 1,479 genes differed significantly at baseline of treatment. Suprabasin (SBSN) was identified as a potential biomarker to predict linezolid-associated neuropathy. In the validation cohort, 10 of 42 (23.8%) patients developed grade ≥3 neuropathies. The area under the curve for the biomarker algorithm prediction of grade ≥3 neuropathies was 0.63 (poor; 95% confidence interval: 0.42 - 0.84). CONCLUSIONS: We identified and preliminarily validated a potential clinical biomarker to predict linezolid-associated neuropathies before the initiation of MDR/RR-TB therapy. Larger studies of the SBSN biomarker in more diverse populations are warranted.

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PMID: 38939039

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

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OBJECTIVES: We sought to capture the evolutionary itinerary of the Mycobacterium

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

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9. A composite reference standard is needed for bedaquiline antimicrobial susceptibility testing for Mycobacterium tuberculosis complex.

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Comment on
Eur Respir J. 2023 Dec 14;62(6):2300639. doi: 10.1183/13993003.00639-2023.

A composite reference standard minimises false-susceptible AST results for bedaquiline https://bit.ly/3wAVvFm

We echo the latest calls that have been made to increase the capacity for antimicrobial susceptibility testing (AST) for bedaquiline for the Mycobacterium tuberculosis complex [1, 2]. However, we would like to highlight the limitations of using insufficiently standardised or validated phenotypic AST methods and

breakpoints as the reference standard for bedaquiline AST. Moreover, we advocate for adoption of a composite reference standard that considers genotypic AST results to minimise false-susceptible results for borderline/low-level resistance mechanisms and avoid confusion during clinical decision-making.

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10. Acupuncture as adjunctive treatment for linezolid-induced peripheral neuropathy: a case series report.

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BACKGROUND: The treatment of multidrug-resistant tuberculosis (MDR-TB) and pre-extensively drug-resistant tuberculosis (pre-XDR-TB) remains challenging due to the limited availability of effective drugs. Linezolid has emerged as a promising therapeutic option for these cases. However, its long-term use can lead to complications such as peripheral and optic neuropathies. Acupuncture, a cornerstone of traditional Chinese medicine, has been shown to be effective in the treatment of peripheral neuropathy (PN). This study examines the potential benefits of acupuncture in the treatment of linezolid-induced peripheral neuropathy (LIPN).
METHODS: Four patients, aged 27 to 60 years, diagnosed with LIPN, underwent daily acupuncture treatments. The main endpoint was to assess the efficacy of acupuncture in reducing neuropathic pain associated with LIPN in patients. This was primarily measured using changes in the Short Form McGill Pain Questionnaire (SF-MPQ) scores before and after acupuncture treatment.
RESULTS: Three of the patients experienced significant symptom remission, while one experienced marginal improvement. Treatments ranged from 7 to 18 sessions. Specifically, the first patient reported substantial relief with a score reduction from 33 to 13; the second patient observed minimal change; the third patient's score decreased dramatically from 10 to 2 after eight sessions; the last patient had a score reduction from 21 to 12 after five sessions, but did not continue treatment for a second assessment.
CONCLUSION: Acupuncture is a promising therapeutic approach for LIPN. However, larger and more thorough studies are needed to determine its full potential.

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PMID: 38974688

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.

11. Assessing the quality of life in patients with drug-resistant tuberculosis: a cross-sectional study.

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BACKGROUND: This study investigated the current status of the quality of life (QOL) of drug-resistant tuberculosis (DR-TB) patients in Nanjing, China, and analyzed the influencing factors.
METHODS: The survey was conducted among patients with DR-TB who were hospitalized in the tuberculosis department of the Second Hospital of Nanjing (Nanjing Public Health Medical Center) from July 2022 to May 2023. The Chinese version of the World Health Organization Quality of Life (WHOQOL-BREF) questionnaire was used to investigate the QOL levels of patients with DR-TB, and a multiple linear regression model was used to analyze the QOL influencing factors.
RESULTS: A total of 135 patients participated in the study; 69.6% were male, the average age was 46.30 ± 17.98 years, 13.33% had an education level of elementary school or below, and 75.56% were married. The QOL scores were 51.35 ± 17.24, 47.04 ± 20.28, 43.89 ± 17.96, and 35.00 ± 11.57 in the physiological, psychological, social, and environmental domains, respectively. The differences between the four domain scores and the Chinese normative results were statistically significant ($P < 0.05$). The results of multiple linear regression analysis showed that the factors related to the physiological domain included residence, family per-capita monthly income, payment method, adverse drug reactions (ADRs), and comorbidities; psychological domain correlates included educational level, family per-capita monthly income, course of the disease, and caregivers; social domain correlates included age and comorbidities; and factors related to the environmental domain included age, education level, and comorbidities.
CONCLUSIONS: In Nanjing, China, patients with younger age, higher education level, living in urban areas, high family per-capita monthly income, no adverse drug reactions, no comorbidities, and having caregivers have better quality of life. Future interventions to improve the quality of life of patients with drug-resistant tuberculosis could be tailored to a specific factor.

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

12. Diagnostic accuracy of the Xpert(®) MTB/XDR assay for detection of Isoniazid and

second-line antituberculosis drugs resistance at central TB reference laboratory in Tanzania.

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INTRODUCTION: Early diagnosis of tuberculosis (TB) and universal access to drug-susceptibility testing (DST) are critical elements of the WHO End TB Strategy. Current rapid tests (e.g., Xpert® MTB/RIF and Ultra-assays) can detect rifampicin resistance-conferring mutations, but cannot detect resistance to Isoniazid and second-line anti-TB agents. Although Line Probe Assay is capable of detecting resistance to second-line anti-TB agents, it requires sophisticated laboratory infrastructure and advanced skills which are often not readily available in settings replete with TB. A rapid test capable of detecting Isoniazid and second-line anti-TB drug resistance is highly needed.
METHODS: We conducted a diagnostic accuracy study to evaluate a new automated Xpert MTB/XDR 10-colour assay for rapid detection of Isoniazid and second-line drugs, including ethionamide, fluoroquinolones, and injectable drugs (Amikacin, Kanamycin, and Capreomycin). Positive Xpert MTB/RIF respiratory specimens were prospectively collected through routine diagnosis and surveillance of drug resistance at the Central TB Reference Laboratory in Tanzania. Specimens were tested by both Xpert XDR assay and LPA against culture-based phenotypic DST as the reference standard.
FINDINGS: We analysed specimens from 151 TB patients with a mean age (SD) of 36.2 (12.7) years. The majority (n = 109, 72.2%) were males. The sensitivity for Xpert MTB/XDR was 93.5% (95% CI, 87.4-96.7); for Isoniazid, 96.6 (95% CI, 92.1-98.6); for Fluoroquinolone, 98.7% (95% Cl 94.8-99.7); for Amikacin, 96.6%; and (95% CI 92.1-98.6) for Ethionamide. Ethionamide had the lowest specificity of 50% and the highest was 100% for Fluoroquinolone. The diagnostic performance was generally comparable to that of LPA with slight variations between the two assays. The non-determinate rate (i.e., invalid M. tuberculosis complex

detection) of Xpert MTB/XDR was 2·96%.
CONCLUSION: The Xpert MTB/XDR demonstrated high sensitivity and specificity for detecting resistance to Isoniazid, Fluoroquinolones, and injectable agents. This assay can be used in clinical settings to facilitate rapid diagnosis of mono-isoniazid and extensively drug-resistant TB.

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PMID: 38965482 [Indexed for MEDLINE]

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

13. Association between HIV and acquisition of rifamycin resistance with first-line TB treatment: a systematic review and meta-analysis.

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BACKGROUND: Multi-drug or rifamycin-resistant tuberculosis (MDR/RR-TB) is an important public health concern, including in settings with high HIV prevalence. TB drug resistance can be directly transmitted or arise through resistance acquisition during first-line TB treatment. Limited evidence suggests that people living with HIV (PLHIV) might have an increased risk of acquired rifamycin-resistance (ARR).
METHODS: To assess HIV as a risk factor for ARR during first-line TB treatment, a systematic review and meta-analysis was conducted. ARR was defined as

rifamycin-susceptibility at treatment start with rifamycin-resistance diagnosed during or at the end of treatment, or at recurrence. PubMed/MEDLINE, CINAHL, Cochrane Library, and Google Scholar databases were searched from inception to 23 May 2024 for articles in English; conference abstracts were also searched from 2004 to 2021. The Mantel-Haenszel random-effects model was used to estimate the pooled odds ratio of any association between HIV and ARR among individuals receiving first-line TB treatment.
RESULTS: Ten studies that included data collected between 1990 and 2014 were identified: five from the United States, two from South Africa and one each from Uganda, India and Moldova. A total of 97,564 individuals were included across all studies, with 13,359 (13.7%) PLHIV. Overall, 312 (0.32%) acquired rifamycin-resistance, among whom 115 (36.9%) were PLHIV. The weighted odds of ARR were 4.57 (95% CI, 2.01-10.42) times higher among PLHIV compared to HIV-negative individuals receiving first-line TB treatment.
CONCLUSION: The available data, suggest that PLHIV have an increased ARR risk during first-line TB treatment. Further research is needed to clarify specific risk factors, including advanced HIV disease and TB disease severity. Given the introduction of shorter, 4-month rifamycin-based regimens, there is an urgent need for additional data on ARR, particularly for PLHIV.
SYSTEMATIC REVIEW REGISTRATION: PROSPERO CRD42022327337.

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PMID: 38956461 [Indexed for MEDLINE]

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14. Trend of pulmonary tuberculosis and rifampicin-resistance among tuberculosis presumptive patients in Central Tigray, Ethiopia; 2018 -2023: a six-year retrospective study.

Trop Dis Travel Med Vaccines. 2024 Jul 1;10(1):15. doi: 10.1186/s40794-024-00224-1.

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BACKGROUND: Tuberculosis (TB) is a major public health concern in the developing countries. Moreover, the emergence of multidrug-resistant tuberculosis is challenging. However, there are no organized data on the trends of pulmonary tuberculosis and rifampicin-resistant Mycobacterium tuberculosis in the study area.
METHODS: A retrospective cross-sectional study was conducted to fill the information gap in Central Tigray at St. Mary General Hospital between 2018 and 2023. Data were collected from the GeneXpert™ tuberculosis registration logbooks using standard checklists and analyzed using Statistical Package for Social Science version 22. After performing logistic regression, a p-value < 0.05 with a corresponding 95% confidence interval was considered statistically significant. Moreover, chi square test for trend was performed to assess the percentage of annual detection of pulmonary tuberculosis and rifampicin-resistant Mycobacterium tuberculosis during the study years.
RESULT: Presumptive pulmonary tuberculosis patients with complete data (n = 3696) were included in the study. The overall prevalence of pulmonary tuberculosis was 11.7%, of which 8.1% were resistant to rifampicin. The study revealed that the incidence of pulmonary tuberculosis has been increasing, mainly in the recent four years. Likewise, an increase in rifampicin-resistant Mycobacterium tuberculosis was observed with considerable fluctuations. Age, human immunodeficiency virus infection, and presumptive rifampicin-resistant Mycobacterium tuberculosis infection were significantly associated with the presence of pulmonary tuberculosis. Moreover, pulmonary tuberculosis was more prevalent among participants in the productive-age group.
CONCLUSION: Although there have been fluctuations, an increasing of pulmonary tuberculosis and rifampicin-resistant Mycobacterium tuberculosis has been observed in recent years. Hence, prevention and treatment strategies for tuberculosis should be strengthened to alleviate the burden of pulmonary tuberculosis and rifampicin-resistant Mycobacterium tuberculosis in the study area.

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PMID: 38946006

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

15. How much should we still worry about QTc prolongation in rifampicin-resistant tuberculosis? ECG findings from TB-PRACTECAL clinical trial.

Antimicrob Agents Chemother. 2024 Jul 9;68(7):e0053624. doi: 10.1128/aac.00536-24. Epub 2024 Jun 6.

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Regimens for the treatment of rifampicin-resistant tuberculosis currently rely on the use of QT-prolonging agents. Using data from the randomized controlled trial, TB-PRACTECAL, we investigated differences in QTcF among participants in the three interventional arms: BPaL (bedaquiline, pretomanid, and linezolid), BPaLC (BPaL with clofazimine), and BPaLM (BPaL with moxifloxacin). Additionally, we assessed whether age, body mass index, and country were causally associated with QTcF prolongation. The trial included participants from South Africa, Uzbekistan, and Belarus. A post hoc analysis of electrocardiogram data was undertaken. Random effects regression was used to model QTcF longitudinally over 24 weeks and causal frameworks guided the analysis of non-randomized independent variables. 328 participants were included in BPaL-based arms. The longitudinal analysis of investigational arms showed an initial QTcF steep increase in the first week. QTcF trajectories between weeks 2 and 24 differed slightly by

regimen, with highest mean peak for BPaLC (QTcF 446.5 ms). Overall, there were 397 QTcF >450 ms (of 3,744) and only one QTcF >500 ms. The odds of QTcF >450 ms among participants in any investigational arm, was 8.33 times higher in Uzbekistan compared to Belarus (95% confidence interval: 3.25-21.33). No effect on QTcF prolongation was found for baseline age or body mass index (BMI). Clinically significant QTc prolongation was rare in this cohort of closely monitored participants. Across BPaL-based regimens, BPaLC showed a slightly longer and sustained effect on QTcF prolongation, but the differences (both in magnitude of change and trajectory over time) were clinically unimportant. The disparity in the risk of QTc prolongation across countries would be an important factor to further investigate when evaluating monitoring strategies.
CLINICAL TRIALS: This study is registered with ClinicalTrials.gov as NCT02589782.

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PMID: 38842323 [Indexed for MEDLINE]

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

16. Define SNP thresholds for delineation of tuberculosis transmissions using whole-genome sequencing.

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For facilitating tuberculosis (TB) control, we used a whole-genome sequencing (WGS)-based approach to delineate transmission networks in a country with an intermediate burden of TB. A cluster was defined as Mycobacterium tuberculosis isolates with identical genotypes, and an outbreak was defined as clustered cases with epidemiological links (epi-links). To refine a cluster predefined using space oligonucleotide typing and mycobacterial interspersed repetitive unit variable tandem repeat typing, we analyzed one pansusceptible TB (C1) and three multidrug-resistant (MDR)-TB (C2-C4) clusters from different scenarios. Pansusceptible TB cluster (C1) consisting of 28 cases had ≤5 single nucleotide polymorphisms (SNPs) difference between their isolates. C1 was a definite outbreak, with cases attending the same junior high school in 2012. Three MDR-TB clusters (C2-C4) with distinct genotypes were identified, each consisting of

12-22 cases. Some of the cases had either ≤5 or ≤15 SNPs difference with clear or probable epi-links. Of note, even though WGS could effectively assist TB contact tracing, we still observed missing epi-links in some cases within the same cluster. Our results showed that thresholds of ≤5 and ≤15 SNPs difference between isolates were used to categorize definite and probable TB transmission, respectively. Furthermore, a higher SNP threshold might be required to define an MDR-TB outbreak. WGS still needs to be combined with classical epidemiological methods for improving outbreak investigations. Importantly, different SNP thresholds have to be applied to define outbreaks.
IMPORTANCE: TB is a chronic disease. Depending on host factors and TB burden, clusters of cases may continue to increase for several years. Conventional genotyping methods overestimate TB transmission, hampering precise detection of outbreaks and comprehensive surveillance. WGS can be used to obtain SNP information of M. tuberculosis to improve discriminative limitations of conventional methods and to strengthen delineation of transmission networks. It is important to define the country-specific SNP thresholds for investigation of transmission. This study demonstrated the use of thresholds of ≤5 and ≤15 SNPs difference between isolates to categorize definite and probable transmission, respectively. Different SNP thresholds should be applied while a higher cutoff was required to define an MDR-TB outbreak. The utilization of SNP thresholds proves to be crucial for guiding public health interventions, eliminating the need for unnecessary public health actions, and potentially uncovering undisclosed TB transmissions.

DOI: 10.1128/spectrum.00418-24
PMID: 38916321

17. Impact of bedaquiline regimen on the treatment success rates of multidrug-resistant tuberculosis patients in Egypt.

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Bedaquiline (BDQ), an innovative anti-tuberculous (TB) agent, has attracted attention for its potential effectiveness against drug-resistant TB. This study investigated the impact of BDQ-containing regimens on treatment success rates among multi-drug resistant tuberculosis (MDR-TB) patients in Egypt. We conducted a prospective cohort study that included all adult non-pregnant patients treated in MDR-TB centers in Egypt from April 1, 2020, to June 30, 2021, with follow-up extended until December 31, 2022. The study compared patients prescribed BDQ according to national protocols with those receiving conventional treatments for MDR-TB. Treatment success rates, mortality rates, and adverse events were analyzed using descriptive statistics, chi-square tests, logistic regression, and Kaplan-Meier survival curves. Adjustment for potential confounders was conducted using propensity score matching and Cox-hazard regressions. A total of 84 patients were included in this study. The median age of the study participants was 39 years; 22.6% were women, 57.1% were unemployed or housewives, and 1.2% had human immunodeficiency virus (HIV). Regarding the treatment regimen, 67.8% were exposed to BDQ-based treatment. Among the 55 patients (65.5%) with treatment success, a significantly higher success rate was observed in the BDQ group (73.7%) compared to the conventional group (48.1%), P = 0.042. Additionally, the incidence of skin discoloration was significantly higher in the BDQ group compared to the conventional group (38.6% versus 0.0%, P < 0.001). Despite the lower mortality incidence in the BDQ-group (14.0% versus 22.2% in the conventional group), the Kaplan-Meier survival analysis revealed no excess mortality associated with the BDQ-group, with a hazard ratio (HR) of 0.62 (95% CI 0.21-1.78, P = 0.372). Propensity score matching, while considering factors such as lesion site, diabetes mellitus, hepatitis C virus, and smoking, revealed a significant increase in the success rate associated with BDQ inclusion, with an HR of 6.79 (95% CI 1.8-25.8). In conclusion, BDQ is an effective and tolerable medication for treating MDR-TB, associated with lower mortality rates compared to conventional treatment.

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

18. Trends in the availability and prices of quality-assured tuberculosis drugs: a systematic analysis of Global Drug Facility Product Catalogs from 2001 to 2024.

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BACKGROUND: The Global Drug Facility (GDF) of the Stop TB Partnership was launched in 2001 with the goal of increasing access to quality-assured tuberculosis (TB) drugs and products. We aimed to describe the TB drugs and prices available from the GDF over time and to assess trends.
METHODS: We searched the internet, including an internet archive, for past and recent GDF Product Catalogs and extracted the listed TB drugs and prices. We calculated the lowest price for the most common drug formulations assuming drugs with similar active pharmaceutical ingredients (APIs) are substitutes for each other. We assessed time trends in the TB drugs and prices offered by the GDF in univariable regressions over the longest possible period.
RESULTS: We identified 43 different GDF Product Catalogs published between November 2001 and May 2024. These product catalogs included 122 single medicines (31 APIs), 28 fixed-dose combinations (9 API combinations), and 8 patient kits (8 API regimens and other materials). The number of TB drugs listed in the GDF Product Catalog increased from 9 (8 APIs) to 55 (32 APIs). The price decreased for 17, increased for 19, and showed no trend for 12 APIs. The price of 15 (53.6%) of 28 APIs used against drug-resistant TB decreased, including the price of drugs used in new treatment regimens. The decreasing price trend was strongest for linezolid (-16.60 [95% CI: -26.35 to -6.85] percentage points [pp] per year), bedaquiline (-12.61 [95% CI: -18.00 to -7.22] pp per year), cycloserine (-11.20 [95% CI: -17.40 to -4.99] pp per year), pretomanid (-10.47 [95% CI: -15.06 to -5.89] pp per year), and rifapentine (-10.46 [95% CI: -12.86 to -8.06] pp per year). The prices of 16 (61.5%) of 23 APIs for standard drug-susceptible TB treatment increased, including rifampicin (23.70 [95% CI: 18.48 to 28.92] pp per year), isoniazid (20.95 [95% CI: 18.96 to 22.95] pp per year), ethambutol (9.85 [95% CI: 8.83 to 10.88] pp per year), and fixed-dose combinations thereof.

CONCLUSIONS: The number of TB drugs available from the GDF has substantially increased during its first 23 years of operation. The prices of most APIs for new TB treatments decreased or remained stable. The prices of most APIs for standard drug-sensitive TB treatment increased.

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19. Cost-effectiveness of interventions for HIV/AIDS, malaria, syphilis, and tuberculosis in 128 countries: a meta-regression analysis.

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BACKGROUND: Cost-effectiveness analyses have been conducted for many interventions for HIV/AIDS, malaria, syphilis, and tuberculosis, but they have not been conducted for all interventions that are currently recommended in all countries. To support national decision makers in the effective allocation of resources, we conducted a meta-regression analysis of published incremental cost-effectiveness ratios (ICERs) for interventions for these causes, and predicted ICERs for 14 recommended interventions for Global Fund-eligible countries.
METHODS: In the meta-regression analysis, we used data from the Tufts University

Center for the Evaluation of Value and Risk in Health (Boston, MA, USA) Cost-Effectiveness Registries (the CEA Registry beginning in 1976 and the Global Health CEA registry beginning in 1995) up to Jan 1, 2018. To create analysis files, we standardised and mapped the data, extracted additional data from published articles, and added variables from the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD). Then we selected ratios for interventions with a minimum of two published articles and three published ICERs that mapped to one of five GBD causes (HIV/AIDS, malaria, syphilis, drug-susceptible tuberculosis, or multi-drug resistant tuberculosis), and to a GBD country; reported a currency year during or after 1990; and for which the comparator intervention was defined as no intervention, standard of care, or placebo. Our meta-regression analysis used all available data on 25 eligible interventions, and quantified the association between ICERs and factors at country level and intervention level. We used a five-stage statistical model that was developed to synthesise evidence on cost-effectiveness analyses, and we adapted it for smaller sample sizes by grouping interventions by cause and type (ie, prevention, diagnostics, and treatment). Using the meta-regression parameters we predicted country-specific median ICERs, IQRs, and 95% uncertainty intervals in 2019 US$ per disability-adjusted life-year (DALY) for 14 currently recommended interventions. We report ICERs in league tables with gross domestic product (GDP) per capita and country-specific thresholds.

FINDINGS: The sample for the analysis was 1273 ratios from 144 articles, of which we included 612 ICERs from 106 articles in our meta-regression analysis. We predicted ICERs for antiretroviral therapy for prevention for two age groups and pregnant women, pre-exposure prophylaxis against HIV for two risk groups, four malaria prevention interventions, antenatal syphilis screening, two tuberculosis prevention interventions, the Xpert tuberculosis test, and chemotherapy for drug-sensitive tuberculosis. At the country level, ranking of interventions and number of interventions with a predicted median ICER below the country-specific threshold varied greatly. For instance, median ICERs for six of 14 interventions were below the country-specific threshold in Sudan, whereas 12 of 14 were below the country-specific threshold in Peru. Antenatal syphilis screening had the lowest median ICER among all 14 interventions in 81 (63%) of 128 countries, ranging from $3 (IQR 2-4) per DALY averted in Equatorial Guinea to $3473 (2244-5222) in Ukraine. Pre-exposure prophylaxis for HIV/AIDS for men who have sex with men had the highest median ICER among all interventions in 116 (91%) countries, ranging from $2326 (1077-4567) per DALY averted in Lesotho to $53 559 (23 841-108 534) in Maldives.

INTERPRETATION: Country-specific league tables highlight the interventions that offer better value per DALY averted, and can support decision making at a country level that is more tailored to available resources than GDP per capita and country-specific thresholds. Meta-regression is a promising method to synthesise cost-effectiveness analysis results and transfer them across settings.

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20. Evaluation of WHO catalog of mutations and five WGS analysis tools for drug resistance prediction of Mycobacterium tuberculosis isolates from China.

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The continuous advancement of molecular diagnostic techniques, particularly whole-genome sequencing (WGS), has greatly facilitated the early diagnosis of drug-resistant tuberculosis patients. Nonetheless, the interpretation of results from various types of mutations in drug-resistant-associated genes has become the primary challenge in the field of molecular drug-resistance diagnostics. In this study, our primary objective is to evaluate the diagnosis accuracy of the World Health Organization (WHO) catalog of mutations and five WGS analysis tools (PhyResSE, Mykrobe, TB Profiler, Gen-TB, and SAM-TB) in drug resistance to 10 anti-Mycobacterium tuberculosis (MTB) drugs. We utilized the data of WGS

collected between 2014 and 2017 in Zhejiang Province, consisting of 110 MTB isolates as detailed in our previous study. Based on phenotypic drug susceptibility testing (DST) results using the proportion method on Löwenstein-Jensen medium with antibiotics, we evaluated the predictive accuracy of genotypic DST obtained by these tools. The results revealed that the WHO catalog of mutations and five WGS analysis tools exhibit robust predictive capabilities concerning resistance to isoniazid, rifampicin, ethambutol, streptomycin, amikacin, kanamycin, and capreomycin. Notably, Mykrobe, SAM-TB, and TB Profiler demonstrate the most accurate predictions for resistance to pyrazinamide, prothionamide, and para-aminosalicylic acid, respectively. These findings are poised to significantly guide and influence future clinical treatment strategies and resistance monitoring protocols.IMPORTANCEWhole-genome sequencing (WGS) has the potential for the early diagnosis of drug-resistant tuberculosis. However, the interpretation of mutations of drug-resistant-associated genes represents a significant challenge as the amount and complexity of WGS data. We evaluated the accuracy of the World Health Organization catalog of mutations and five WGS analysis tools in predicting drug resistance to first-line and second-line anti-TB drugs. Our results offer clinicians guidance on selecting appropriate WGS analysis tools for predicting resistance to specific anti-TB drugs.

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21. Clinical effects of detailed nursing management interventions on medication adherence and disease perception in patients with drug-resistant tuberculosis.

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BACKGROUND: Tuberculosis (TB) is a chronic respiratory infectious disease that considerably jeopardizes human health, and there is no effective vaccine suitable for its prevention in the entire population.
AIM: To investigate the promotion of medication adherence and disease cognition in patients with drug-resistant (DR-)TB using detailed nursing management.
METHODS: In total, 114 patients with DR-TB who were diagnosed and treated at our

hospital between January 2019 and January 2023 were included in this study. Patients in the control group (n = 57) were managed with conventional nursing care, while those in the observation group (n = 57) were managed with detailed nursing care. Medication adherence, disease awareness scores, medication safety, and nursing satisfaction were compared between the two groups after the intervention.
RESULTS: The post-intervention medication compliance rate was 91.23% in the observation group and 75.44% in the control group, with the former being 15.79% higher than the latter ($P < 0.05$). There was no statistically significant difference in the disease awareness scores between the two groups before the intervention; the disease awareness scores of the observation group were significantly higher than those of the control group after the intervention ($P < 0.05$). The incidence of gastrointestinal reactions, joint swelling and pain, hearing loss, electrolyte disorders, and liver and kidney function abnormalities were lower in the observation group than those in the control group. The total nursing satisfaction of the observation group was higher than that of the control group ($P < 0.05$).
CONCLUSION: Implementation of detailed nursing management for patients with DR-TB can effectively improve medication adherence, enhance awareness of the disease, ensure safety of medication, and improve satisfaction with nursing care.

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PMID: 39015906

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22. A blood-based 3-gene signature score for therapeutic monitoring in patients with pulmonary tuberculosis.

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OBJECTIVE: To assess the validity of Xpert Tuberculosis Fingerstick score for monitoring treatment response and analyze factors influencing its performance.
METHODS: 122 adults with pulmonary tuberculosis were recruited and stratified into three cohorts: Diabetic-drug-susceptible-TB (DM-TB), Non-diabetic-drug-susceptible-TB (NDM-TB) and Non-diabetic Multidrug-resistant TB (MDR-TB). Fingerstick blood specimens were tested at treatment initiation (M0) and the end of the first (M1), second (M2), and sixth month (M6) to generate a TB-score.
RESULTS: The TB-score in all participants yielded an AUC of 0.707 (95% CI: 0.579-0.834) at M2 when its performance was evaluated against sputum culture conversion. In all non-diabetes patients, the AUC reached 0.88 (95% CI: 0.756-1.000) with an optimal cut-off value of 1.95 at which sensitivity was 90.0% (95% CI: 59.6-98.2%) and specificity was 81.3% (95% CI: 70.0-88.9%). The mean TB score was higher in patients with low bacterial loads (n = 31) than those with high bacterial loads (n = 91) at M0, M1, M2, and M6, and was higher in non-cavitary patients (n = 71) than those with cavitary lesions (n = 51) at M0, M1, and M2.
CONCLUSION: Xpert TB-score shows promising predictive value for culture conversion in non-diabetic TB patients. Sputum bacterial load and lung cavitation status have an influence on the value of TB score.

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23. Genomic and spatial analysis reveal the transmission dynamics of tuberculosis in areas with high incidence of Zhejiang, China: A prospective cohort study.

Infect Genet Evol. 2024 Jul;121:105603. doi: 10.1016/j.meegid.2024.105603. Epub 2024 May 8.

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In the mountainous, rural regions of eastern China, tuberculosis (TB) remains a formidable challenge; however, the long-term molecular epidemiological surveillance in these regions is limited. This study aimed to investigate molecular and spatial epidemiology of TB in two mountainous, rural counties of Zhejiang Province, China, from 2015 to 2021, to elucidate the recent transmission and drug-resistance profiles. The predominant Lineage 2 (L2) Beijing family accounted for 80.1% of total 532 sequenced Mycobacterium tuberculosis (Mtb) strains, showing consistent prevalence over seven years. Gene mutations associated with drug resistance were identified in 19.4% (103/532) of strains, including 47 rifampicin or isoniazid-resistant strains, eight multi-drug-resistant (MDR) strains, and five pre-extensively drug-resistant (pre-XDR) strains. Genomic clustering revealed 53 distinct clusters with an overall transmission clustering rate of 23.9% (127/532). Patients with a history of retreatment and those infected with L2 strains had a higher risk of recent transmission. Spatial and epidemiological analysis unveiled significant

transmission hotspots, especially in densely populated urban areas, involving various public places such as medical institutions, farmlands, markets, and cardrooms. The study emphasizes the pivotal role of Beijing strains and urban-based TB transmission in the western mountainous regions in Zhejiang, highlighting the urgent requirement for specific interventions to mitigate the impact of TB in these unique communities.

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24. Holistic acceptability of an adult levofloxacin formulation in children and adolescents on a tuberculosis preventive treatment trial.

PLOS Glob Public Health. 2024 Jul 5;4(7):e0003381. doi: 10.1371/journal.pgph.0003381. eCollection 2024.

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Drug-resistant tuberculosis (TB) is threatening global TB control. Although formulations designed for children are a priority, adult levofloxacin formulations are widely used in TB treatment and prevention. TB-CHAMP was a cluster-randomised, placebo-controlled trial evaluating the efficacy and safety of 24 weeks of daily levofloxacin to prevent TB in child and adolescent household contacts of adults with infectious multidrug-resistant TB. Nested in-depth longitudinal qualitative work was conducted in a subset of children and their caregivers to understand broader experiences of treatment acceptability. We conducted 41 interviews with 8 caregivers of children <6 years, and with 6 older children responding for themselves. Children who could not swallow the adult formulation whole, found the tablet unpalatable, although they learnt to tolerate the taste over time. Most caregivers and children came from families with substantial experience of TB, but felt they knew little about TB preventive therapy. Many families experienced challenging socio-economic circumstances. Poor acceptability was mitigated by sympathetic study personnel, assistance with

transport and financial compensation. The adult formulation of levofloxacin was disliked by many younger children but was acceptable to children able to swallow the tablet whole. In addition to using acceptable drug formulations, TB preventive treatment implementation models should include patient education and should accommodate patients' socioeconomic challenges.

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PMID: 38968182

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

25. Comparison of microscopic and xpert MTB diagnoses of presumptive mycobacteria tuberculosis infection: retrospective analysis of routine diagnosis at Cape Coast Teaching Hospital.

BMC Infect Dis. 2024 Jul 2;24(1):660. doi: 10.1186/s12879-024-09566-9.

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INTRODUCTION: Tuberculosis is a global health problem that causes 1. 4 million deaths every year. It has been estimated that sputum smear-negative diagnosis but culture-positive pulmonary TB diagnosis contribute to 12.6% of pulmonary TB transmission. TB diagnosis by smear microscopy smear has a minimum detection limit (LOD) of 5,000 to 10,000 bacilli per milliliter (CFU/ml) of sputum result in missed cases and false positives. However, GeneXpert technology, with a LOD of 131-250 CFU/ml in sputum samples and its implementation is believe to facilitate early detection TB and drug-resistant TB case. Since 2013, Ghana health Service (GHS) introduce GeneXpert MTB/RIF diagnostic in all regional hospitals in Ghana, however no assessment of performance between microscopy and GeneXpert TB diagnosis cross the health facilities has been reported. The study compared the results of routine diagnoses of TB by microscopy and Xpert MTB from 2016 to 2020 at the Cape Coast Teaching Hospital (CCTH).
METHODS: The study compared routine microscopic and GeneXpert TB diagnosis results at the Cape Coast Teaching Hospital (CCTH) from 2016 to 2020 retrospectively. Briefly, sputum specimens were collected into 20 mL sterile screw-capped containers for each case of suspected TB infection and processed within 24 h. The samples were decontaminated using the NALC-NaOH method with the final NaOH concentration of 1%. The supernatants were discarded after the centrifuge and the remaining pellets dissolved in 1-1.5 ml of phosphate buffer saline (PBS) and used for diagnosis. A fixed smears were Ziehl-Neelsen acid-fast stain and observed under microscope and the remainings were used for GeneXpert MTB/RIF diagnosis. The data were analyze using GraphPad Prism.
RESULTS: 50.11% (48.48-51.38%) were females with an odd ratio (95% CI) of 1.004 (0.944-1.069) more likely to report to the TB clinic for suspected TB diagnosis. The smear-positive cases for the first sputum were 6.6% (5.98-7.25%), and the second sputum was 6.07% (5.45-6.73%). The Xpert MTB-RIF diagnosis detected 2.93% (10/341) (1.42-5.33%) in the first and 5.44% (16/294) (3.14-8.69%) in the second smear-negative TB samples. The prevalence of Xpert MTB-RIF across smear positive showed that males had 56.87% (178/313) and 56.15% (137/244) and females had 43.13% (135/313) and 43.85% (107/244) for the first and second sputum. Also, false negative smears were 0.18% (10/5607) for smear 1 and 0.31% (16/5126) for smear 2.
CONCLUSION: In conclusion, the study highlights the higher sensitivity of the GeneXpert assay compared to traditional smear microscopy for detecting MTB. The GeneXpert assay identified 10 and 16 positive MTB from smear 1 and smear 2 samples which were microscopic negative.

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

26. Successful Multidisciplinary Treatment of Small Bowel Obstruction With an Ileal Stricture Resulting in Bowel Perforation in the Setting of Multidrug-Resistant Gastrointestinal Tuberculosis: A Case Report.

Cureus. 2024 Jul 11;16(7):e64353. doi: 10.7759/cureus.64353. eCollection 2024 Jul.

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We present the case of a male in his 40s who recently emigrated from Russia and was actively undergoing treatment for multidrug-resistant (MDR) pulmonary tuberculosis (TB) with the BPaL-M (bedaquiline, pretomanid, linezolid, moxifloxacin, and pyridoxine) regimen who presented to the emergency department (ED) with abdominal pain, vomiting, and no bowel movements. A computed tomography (CT) scan of the abdomen and pelvis revealed a small bowel obstruction (SBO) from ileal stricture consistent with gastrointestinal (GI) TB. He did not require an emergent surgical intervention and was managed conservatively via bowel rest and initiation of total parenteral nutrition (TPN). An oral BPaL-M regimen was held and an intravenous (IV) regimen consisting of linezolid, moxifloxacin, meropenem, and ampicillin/sulbactam was started per infectious disease (ID) recommendations. He improved clinically over the next several days and was started on a diet that was initially well tolerated. Shortly after transitioning to a regular diet, he developed severe abdominal pain. A CT scan of the abdomen and pelvis revealed pneumoperitoneum and he was taken emergently to the operating room (OR) for exploratory laparotomy (ex-lap). A perforation was found in the terminal ileum and he underwent a right hemicolectomy. He returned to the OR two days later for ileocolic anastomosis and fascial closure. A diet was initiated once again which was tolerated well. He was then transitioned back to his oral BPaL-M regimen which was also tolerated well. He was discharged home on an oral diet after a 23-day hospital course with follow-up appointments with acute care surgery (ACS) and ID.

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PMID: 39007023

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27. First detection of a Mycobacterium tuberculosis XDR clinical isolate harbouring an RpoB I491F mutation in a Ukrainian patient treated in Germany, October 2023.

Euro Surveill. 2024 Jul;29(28):2400420. doi: 10.2807/1560-7917.ES.2024.29.28.2400420.

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This report documents the case of a Ukrainian patient infected with an extensively drug-resistant (XDR) lineage 2 Mycobacterium tuberculosis strain harbouring the rifampicin resistance mutation RpoB I491F. This mutation is not detected by routine molecular WHO-recommended rapid diagnostics, complicating the detection and treatment of these strains. The occurrence of such mutations

underscores the need for enhanced diagnostic techniques and tailored treatment regimens, especially in eastern Europe where lineage 2 strains and XDR-tuberculosis are prevalent.

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PubMed Non-Open Access

28. Pharmacovigilance in Pregnancy Studies, Exposures and Outcomes Ascertainment, and Findings from Low- and Middle-Income Countries: A Scoping Review.

Drug Saf. 2024 Jun 21. doi: 10.1007/s40264-024-01445-1. Online ahead of print.

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INTRODUCTION: Pharmacovigilance (PV), or the ongoing safety monitoring after a medication has been licensed, plays a crucial role in pregnancy, as clinical trials often exclude pregnant people. It is important to understand how pregnancy PV projects operate in low- and middle-income countries (LMICs), where there is a disproportionate lack of PV data yet a high burden of adverse pregnancy outcomes. We conducted a scoping review to assess how exposures and outcomes were measured in recently published pregnancy PV projects in LMICs.
METHODS: We utilized a search string, secondary review, and team knowledge to review publications focusing on therapeutic or vaccine exposures among pregnant people in LMICs. We screened abstracts for relevance before conducting a full text review, and documented measurements of exposures and outcomes (categorized as maternal, birth, or neonatal/infant) among other factors, including study topic, setting, and design, comparator groups, and funding sources.
RESULTS: We identified 31 PV publications spanning at least 24 LMICs, all

focusing on therapeutics or vaccines for infectious diseases, including HIV (n = 17), tuberculosis (TB; n = 9), malaria (n = 7), pertussis, tetanus, and diphtheria (n = 1), and influenza (n = 3). As for outcomes, n = 15, n = 31, and n = 20 of the publications covered maternal, birth, and neonatal/infant outcomes, respectively. Among HIV-specific publications, the primary exposure-outcome relationship of focus was exposure to maternal antiretroviral therapy and adverse outcomes. For TB-specific publications, the main exposures of interest were second-line drug-resistant TB and isoniazid-based prevention therapeutics for pregnant people living with HIV. For malaria-specific publications, the primary exposure-outcome relationship of interest was antimalarial medication exposure during pregnancy and adverse outcomes. Among vaccine-focused publications, the exposure was assessed during a specific time during pregnancy, with an overall interest in vaccine safety and/or efficacy. The study settings were frequently from Africa, designs varied from cohort or cross-sectional studies to clinical trials, and funding sources were largely from high-income countries.
CONCLUSION: The published pregnancy PV projects were largely centered in Africa and concerned with infectious diseases. This may reflect the disease burden in LMICs but also funding priorities from high-income countries. As the prevalence of non-communicable diseases increases in LMICs, PV projects will have to broaden their scope. Birth and neonatal/infant outcomes were most reported, with fewer reporting on maternal outcomes and none on longer-term child outcomes; additionally, heterogeneity existed in definitions and ascertainment of specific measures. Notably, almost all projects covered a single therapeutic exposure, missing an opportunity to leverage their projects to cover additional exposures, add scientific rigor, create uniformity across health services, and bolster existing health systems. For many publications, the timing of exposure, specifically by trimester, was crucial to maternal and neonatal safety. While currently published pregnancy PV literature offer insights into the PV landscape in LMICs, further work is needed to standardize definitions and measurements, integrate PV projects across health services, and establish longer-term monitoring.

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29. Current Epidemiology of Pediatric Tuberculosis.

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Tuberculosis (TB) is a communicable disease that is a major cause of ill health and one of the leading causes of death worldwide. Children act as reservoirs of infection out of which future cases develop. Without the successful detection and treatment of TB infection and disease in children, elimination strategies for TB will be ineffective. India has a severe problem with TB in children, which accounts for around 31% of the global pediatric TB load. However, over the past 10 y, children have consistently made up 6-7% of all patients treated yearly under the National Tuberculosis Elimination Programme (NTEP). There is an estimated detection gap of 56% in India, which is the reason for many missed cases of TB in children. Only 3% of children less than 14 y with MDR/RR-TB, are reported from India, which again is an underestimation of the actual incident cases. Population density, housing and living conditions, environmental conditions, cultural practices, age of the child, exposure to tobacco and other environmental pollutants, the virulence of the mycobacterial strain and their genetics, host genetics, BCG vaccination, malnutrition, immunodeficiency are some of the risk factors for TB exposure, infection and disease in children. Understanding the natural history as well as the epidemiology of childhood TB is important to assess which children are the most vulnerable. It would also guide us in understanding the burden of pediatric TB on a regional, national, or global level, thus facilitating the appropriate targeting of health resources and also guiding policy-making decisions.

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

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Delamanid is an anti-tuberculosis drug used for the treatment of drug-resistant tuberculosis. Since delamanid has a high protein bound potential, even patients with low albumin levels should experience high and rapid delamanid clearance. However, the interaction between delamanid and albumin should be better controlled to optimize drug efficacy. This study was designed to evaluate the binding characteristics of delamanid to human serum albumin (HSA) using various methods: fluorescence spectroscopy, circular dichroism (CD), surface plasmon resonance (SPR), and molecular docking simulation. The fluorescence emission band without any shift indicated the interaction was not affected by the polarity of the fluorophore microenvironment. The reduction of fluorescence intensity at 344 nm was proportional to the increment of delamanid concentration as a fluorescence quencher. UV-absorbance measurement at the maximum wavelength (λmax, 280 nm) was evaluated using inner filter effect correction. The HSA conformation change was explained by the intermolecular energy transfer between delamanid and HSA during complex formation. The study, which was conducted at temperatures of 298 K, 303 K, and 310 K, revealed a static quenching mechanism that correlated with a decreased of bimolecular quenching rate constant (kq) and binding constant (Ka) at increased temperatures. The Ka was 1.75-3.16 × 104 M-1 with a specific binding site with stoichiometry 1:1. The negative enthalpy change, negative entropy change, and negative Gibbs free energy change demonstrated an exothermic-spontaneous reaction while van der Waals forces and hydrogen bonds played a vital role in the binding. The molecular displacement approach and molecular docking confirmed that the binding occurred mainly in subdomain IIA, which is a hydrophobic pocket of HSA, with a theoretical binding free energy of -9.33 kcal/mol. SPR exhibited a real time negative sensorgram that resulted from deviation of the reflex angle due to ligand delamanid-HSA complex forming. The binding occurred spontaneously after delamanid was presented to the HSA surface. The SPR mathematical fitting model revealed that the association rate constant (kon) was 2.62 × 108 s-1M-1 and the dissociation rate constant (koff) was 5.65 × 10-3 s-1. The complexes were performed with an association constant (KA) of 4.64 × 1010 M-1 and the dissociation constant (KD)

of 2.15 × 10-11 M. The binding constant indicated high binding affinity and high stability of the complex in an equilibrium. Modified CD spectra revealed that conformation of the HSA structure was altered by the presence of delamanid during preparation of the proliposomes that led to the reduction of secondary structure stabilization. This was indicated by the percentage decrease of α-helix. These findings are beneficial to understanding delamanid-HSA binding characteristics as well as the drug administration regimen.

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31. Bedaquiline: An Insight Into its Clinical Use in Multidrug-Resistant Pulmonary Tuberculosis.

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Every year, the World Health Organization reports 500,000 new cases of drug-resistant tuberculosis (TB), which poses a serious global danger. The increased number of XDR-TB and MDR-TB cases reported worldwide necessitates the use of new therapeutic approaches. The main issues with the antitubercular medications now in use for the treatment of multidrug-resistant tuberculosis are their poor side effect profile, reduced efficacy, and antimicrobial resistance. One possible remedy for these problems is bedaquiline. The need for better treatment strategies is highlighted by the strong minimum inhibitory concentrations that bedaquiline (BDQ), a novel anti-TB medicine, exhibits against both drug-resistant and drug-susceptible TB. Bedaquiline may be able to help with these problems. Bedaquiline is a medication that is first in its class and has a distinct and particular mode of action. Bedaquiline is an ATP synthase inhibitor that is specifically directed against Mycobacterium tuberculosis and some nontuberculous mycobacteria. It is metabolized by CYP3A4. Bedaquiline preclinical investigations revealed intralesional drug biodistribution. The precise intralesional and multi-compartment pharmacokinetics of bedaquiline were obtained using PET bioimaging and high-resolution autoradiography investigations. Reduced CFU counts were observed in another investigation after

a 12-week course of therapy. Meta-analyses and systematic reviews of phase II trials on bedaquiline's efficacy in treating drug-resistant tuberculosis in patients reported higher rates of cure, better culture conversion, and lower death rates when taken in conjunction with a background regimen. Here is a thorough medication profile for bedaquiline to aid medical professionals in treating individuals with tuberculosis.

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

32. Anti-tuberculosis effect of microbiome therapeutic PMC205 in extensively drug-resistant pulmonary tuberculosis in vivo.

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BACKGROUND: Tuberculosis is a highly contagious disease caused by Mycobacterium tuberculosis, and the increase in antibiotic resistance threatens humankind. Therefore, there is an urgent need to develop new anti-tuberculosis drugs that can overcome the limitations of existing drugs. Here, we report the anti-tuberculosis effect of microbiome therapeutic PMC205, a strain of Bacillus subtilis.
METHODS: The anti-tuberculosis activity of probiotics was evaluated in mouse models of lethal and latent pulmonary tuberculosis induced by high or low-dose

infection of the extensively drug-resistant (XDR) strain. Probiotics were administered by inhalation, and the burden of M. tuberculosis in the lungs, along with mortality and clinical observations, were monitored for 12 weeks and 8 months, respectively. For an in-depth understanding, analysis of the microbiome and inflammatory profile of the lung microenvironment and induction of autophagy in vitro were explored.
RESULTS: After inhalation administration of PMC205 for 3 months, the survival rate was 100%, unlike all deaths in the saline-treated group, and the burden of M. tuberculosis in the lungs was reduced by log 1.3 in the 8-month latent tuberculosis model. Moreover, PMC205 induced recovery of disrupted lung microflora, increased butyric acid, and suppressed excessive inflammation. It also promoted autophagy.
CONCLUSIONS: These results confirm PMC205's anti-tuberculosis effect, suggesting that it can be developed as an adjuvant to current antibiotic therapy to solve the drug-resistant tuberculosis problem.

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PMID: 39002701

Conflict of interest statement: Competing Interests None to disclose.

33. How can oral second-line anti-tuberculosis medications be administered to an extremely preterm neonate?

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Congenital pre-extensively drug-resistant tuberculosis is rare, and administration of second-line anti-tuberculosis medications to neonates is challenging due to the small doses required and limited availability of suitable formulations. Paediatric formulations have increasingly become available but may not be readily accessible in all countries. For the extremely preterm and low birth weight neonate, doses equivalent to a fraction of a tablet or capsule are required, with frequent dose adjustment for increasing age and weight during the course of treatment. The pharmaceutical formulation must be suitable for administration via enteral feeding tube and must be free of unsafe excipients. We report on the challenges, considerations and outcome of an extremely

premature neonate with congenital pre-extensively drug-resistant tuberculosis who was successfully treated with second-line anti-tuberculosis medications. Child-friendly formulations were procured where available, and extemporaneous compounding of clofazimine, moxifloxacin and prothionamide oral suspensions was undertaken to enable administration of these medications.

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PMID: 39002972

Conflict of interest statement: Competing interests: None declared.

34. Utilization of Truenat chips in defining XDR, pre-XDR and MDR in tuberculous meningitis.

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SETTING AND OBJECTIVE: To develop and evaluate newer molecular tests that identify drug resistance according to contemporary definitions in Tuberculous meningitis (TBM), the most severe form of EPTB.
DESIGN: 93 cerebrospinal fluid (CSF) specimens [41 culture-positive and 52 culture-negative], were subjected to Truenat MTB Plus assay along with chips for rifampicin, isoniazid, fluoroquinolones and bedaquiline resistance. The performance was compared against phenotypic drug susceptibility testing (pDST), Line probe assay (LPA) and gene sequencing.

RESULTS: Against pDST, Truenat chips had a sensitivity and specificity of 100%; 94.47%, 100%; 94.47%, 100%; 97.14% and 100%; 100%, respectively for rifampicin, isoniazid, fluoroquinolones and bedaquiline. Against LPA, all Truenat chips detected resistant isolates with 100% sensitivity; but 2 cases each of false-rifampicin and false-isoniazid resistance and 1 case of false-fluoroquinolone resistance was reported. Truenat drug chips gave indeterminate results in ~25% cases, which were excluded. All cases reported indeterminate were found to be susceptible by pDST/LPA.
CONCLUSION: The strategic drug resistance chips of Truenat Plus assay can contribute greatly to TB elimination by providing rapid and reliable detection of drug resistance pattern in TBM. Cases reported indeterminate require confirmation by other phenotypic and genotypic methods.

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35. The Impact of the Mycobacterium tuberculosis RDRio Subfamily on Multidrug-Resistant Tuberculosis in Latin America: A Comprehensive Review.

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Latin American region is a high-burden setting for tuberculosis where multidrug-resistant tuberculosis (MDR-TB) is among the main challenge to move forward the End TB Strategy goals. It has been shown that MDR-TB is associated to certain Mycobacterium tuberculosis (MTB) lineages like L2-Beijing sublineage or L4-LAM. Although L2-Beijing is present in South America, the L4 lineage is the most prevalent with values ranging from 75% to 99% depending on the country. Within L4, Latin American-Mediterranean (LAM) family is the most prevalent. Moreover, within LAM, RDRio subfamily is present in high prevalence in several countries in South America like Venezuela or Brazil. RDRio has been associated to MDR-TB in several studies in Brazil but more epidemiological information is

needed for South America. Here we discuss the problem of MDR-TB in Latin America and the potential threat that RDRio could represent. At this time, more molecular epidemiology studies are necessary to improve TB surveillance programs in Latin America by tracking MTB strains potentially responsible for MDR-TB spread.

DOI: 10.4269/ajtmh.24-0073
PMID: 38955162

36. Drug exposure and treatment outcomes in patients with multidrug resistant tuberculosis and diabetes mellitus: A multicenter prospective cohort study from China.

Clin Infect Dis. 2024 Jun 24:ciae329. doi: 10.1093/cid/ciae329. Online ahead of print.

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BACKGROUND: The management of multidrug-resistant tuberculosis (MDR-TB) remains challenging. Treatment outcome is influenced by multiple factors, the specific roles of diabetes and glycemic control remain uncertain. This study aims to assess the impact of glycemic control on drug exposure, to investigate the association between drug exposure and treatment outcomes, and to identify clinically-significant thresholds predictive of treatment outcome, among patients with diabetes.
METHODS: This multicenter prospective cohort study involved patients with confirmed MDR-TB and diabetes. Drug exposure level was estimated by noncompartmental analysis. The minimum inhibitory concentrations were determined for the individual Mycobacterium tuberculosis isolates. The influence of poor glycemic control (hemoglobin A1c $\geq$ 7%) on drug exposure and the associations

between drug exposure and treatment outcome were evaluated by univariate and multivariate analysis. Classification and regression tree analysis was used to identify the drug exposure/susceptibility thresholds.
RESULTS: Among the 131 diabetic participants, 43 (32.8%) exhibited poor glycemic control. Poor glycemic control was independently associated with decreased exposure to moxifloxacin, linezolid, bedaquiline, and cycloserine, but not clofazimine. Additionally, a higher ratio of drug exposure to susceptibility was found to be associated with a favorable MDR-TB treatment outcome. Thresholds predictive of 6-month culture conversion and favorable outcome were bedaquiline AUC/MIC $\geq$ 245 and moxifloxacin AUC/MIC $\geq$ 67, demonstrating predictive accuracy in patients, regardless of their glycemic control status.
CONCLUSIONS: Glycemic control and optimal TB drug exposure are associated with improved treatment outcomes. This dual management strategy should be further validated in randomized controlled trials of patients with MDR-TB and diabetes.

DOI: 10.1093/cid/ciae329
PMID: 38913750

37. Drug Susceptibility and Mutation Profiles in Mycobacterium tuberculosis Isolates from a Tertiary Care Hospital in Kerala, India.

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The rising prevalence of drug-resistant Mycobacterium tuberculosis (MTB) strains poses a significant challenge to global tuberculosis (TB) control efforts. This study aimed to analyze drug resistance patterns and investigate the molecular characteristics of 193 MTB clinical isolates to shed light on the mechanisms of

drug resistance. Of the 193 MTB clinical isolates, 28.5% (n = 53) exhibited mono-drug or multidrug resistance. Pyrazinamide mono-drug resistance (PZAr) was the most prevalent (17%, n = 33), followed by isoniazid mono-drug resistance (3.6%, n = 7). Rifampicin resistance was associated with mutations in the rpoB gene (D435Y, D435V, S450L, L452P). Isoniazid resistance mutations were found in the katG (S315T), inhA (C[-15] T), and ndh (R268H) genes, whereas ethambutol resistance mutations were observed in the embB gene (M306V, M306I, M306L, G406S, Q497R). Surprisingly, 94% of PZAr isolates (n = 31) showed no mutations in the pncA or rpsA genes. The presence of the R268H mutation in the ndh gene, not previously linked to PZAr, was detected in 15% of PZAr isolates (n = 5), suggesting its potential contribution to PZAr in specific cases but not as a predominant mechanism. The specific molecular mechanisms underlying PZAr in the majority of the isolates remain unknown, emphasizing the need for further research to uncover the contributing factors. These findings contribute to the understanding of drug resistance patterns and can guide future efforts in TB control and management.

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38. Apramycin has high in vitro activity against Mycobacterium tuberculosis.

J Med Microbiol. 2024 Jul;73(7). doi: 10.1099/jmm.0.001854.

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Introduction. Aminoglycoside antibiotics such as amikacin and kanamycin are important components in the treatment of Mycobacterium tuberculosis (Mtb) infection. However, more and more clinical strains are found to be aminoglycoside antibiotic-resistant. Apramycin is another kind of aminoglycoside antibiotic that is commonly used to treat infections in animals.Hypothesis. Apramycin may have in vitro activity against Mtb.Aim. This study aims to evaluate the efficacy of apramycin against Mtb in vitro and determine its epidemiological cut-off (ECOFF) value.Methodology. One hundred Mtb isolates, including 17 pansusceptible and 83 drug-resistant tuberculosis (DR-TB) strains, were analysed for apramycin resistance using the MIC assay.Results. Apramycin exhibited significant inhibitory activity against Mtb clinical isolates, with an MIC50 of 0.5 µg ml-1 and an MIC90 of 1 µg ml-1. We determined the tentative ECOFF value as 1 µg ml-1 for apramycin. The resistant rates of multidrug-resistant tuberculosis (MDR-TB), pre-extensively drug-resistant (pre-XDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) strains were 12.12% (4/33), 20.69% (6/29) and 66.67% (14/21), respectively. The rrs gene A1401G is associated with apramycin resistance, as well as the cross-resistance between apramycin and other aminoglycosides.Conclusion. Apramycin shows high in vitro activity against the Mtb clinical isolates, especially the MDR-TB clinical isolates. This encouraging discovery calls for more research on the functions of apramycin in vivo and as a possible antibiotic for the treatment of drug-resistant TB.

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PMID: 38973691 [Indexed for MEDLINE]

39. Recent Biochemical Advances in Antitubercular Drugs: Challenges and Future.

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Tuberculosis (TB) is one of the leading causes of death world-wide after AIDS. It infects around one-third of global population and approximately two million people die annually from this disease because it is a very contagious disease spread by Mycobacterium tuberculosis. The increasing number of drug-resistant strains and the failure of conventional treatments against this strain are the challenges of the coming decades. New therapeutic techniques aim to confirm cure without deterioration, to reduce deaths, contagions and the formation of drug-resistant strains. A plethora of new diagnostic tests are available to diagnose the active tuberculosis, screen latent M. tuberculosis infection, and to identify drug-resistant strains of M. tuberculosis. When effective prevention strategies do not prevail, high rates of early case detection and successive cures to control TB emergence would not be possible. In this review, we discussed the structural features of M. tuberculosis, Multi drug resistance tuberculosis (MDR-TB), extremely drug-resistant tuberculosis (XDR-TB), the mechanism of M. tuberculosis infection, the mode of action of first and second-line antitubercular drugs, the mechanism of resistance to the existing drugs, compounds in preclinical and clinical trial and drugs presently available for the treatment of tuberculosis. Moreover, the new diagnostic techniques to detect M. Tuberculosis are also discussed in this review. </p>.

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PMID: 38919089

40. Exploring rhodanine linked enamine-carbohydrazide derivatives as mycobacterial carbonic anhydrase inhibitors: Design, synthesis, biological evaluation, and molecular docking studies.

Arch Pharm (Weinheim). 2024 Jul;357(7):e2400064. doi: 10.1002/ardp.202400064. Epub 2024 Mar 18.

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With the rise of multidrug-resistant tuberculosis, the imperative for an alternative and superior treatment regimen, incorporating novel mechanisms of action, has become crucial. In pursuit of this goal, we have developed and synthesized a new series of rhodanine-linked enamine-carbohydrazide derivatives, exploring their potential as inhibitors of mycobacterial carbonic anhydrase. The findings reveal their efficacy, displaying notable selectivity toward the mycobacterial carbonic anhydrase 2 (mtCA 2) enzyme. While exhibiting moderate activity against human carbonic anhydrase isoforms, this series demonstrates promising selectivity, positioning these compounds as potential antitubercular agents. Compound 6d was the best one from the series with a Ki value of 9.5 μM toward mtCA 2. Most of the compounds displayed moderate to good inhibition against the Mtb H37Rv strain; compound 11k showed a minimum inhibitory concentration of 1 μg/mL. Molecular docking studies revealed that compounds 6d and 11k show metal coordination with the zinc ion, like classical CA inhibitors.

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

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A rapid and comprehensive drug susceptibility test is essential for eliminating drug resistant tuberculosis. Next generation sequencing (NGS) based susceptibility testing is being explored as a potential substitute for the

conventional phenotypic and genotypic testing methods. However, the adoption of NGS based genotypic susceptibility testing depends on the availability of simple, accurate and efficient analysis tools. This preliminary study aimed to evaluate the performance of a Mycobacterium tuberculosis (Mtb) genome analysis pipeline, AAICare®-TB, for susceptibility prediction, in comparison to two widely used gDST prediction tools, TB-Profiler and Mykrobe. This study was performed in a National Reference Laboratory in India on presumptive drug-resistant tuberculosis (DR-TB) isolates. Whole genome sequences of the 120 cultured isolates were obtained through Illumina sequencing on a MiSeq platform. Raw sequences were simultaneously analysed using the three tools. Susceptibility prediction reports thus generated, were compared to estimate the total concordance and discordance. WHO mutation catalogue (1st edition, 2021) was used as the reference standard for categorizing the mutations. In this study, AAICare®-TB was able to predict drug resistance status for First Line (Streptomycin, Isoniazid, Rifampicin, Ethambutol and Pyrazinamide) and Second Line drugs (Fluoroquinolones, Second Line Injectables and Ethionamide) in 93 samples along with lineage and hetero-resistance as per the WHO guidelines.

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PMID: 38744006 [Indexed for MEDLINE]

42. Tuberculosis impacts multiple aspects in quality of life in a Romanian cohort of drug-susceptible and drug resistant patients: A patient-reported outcome measures study.

Trop Med Int Health. 2024 Jul;29(7):584-593. doi: 10.1111/tmi.13996. Epub 2024 May 24.

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BACKGROUND: Tuberculosis (TB), and especially its drug resistant forms, is responsible for not only significant mortality, but also considerable morbidity, still under-quantified. This study used four Patient-Reported Outcome Measures (PROMS) to assess the status of persons affected by drug-susceptible and drug-resistant TB during their TB treatment or after treatment completion, in Romania, the highest TB burden country in the EU.
METHODS: People affected by TB in two different regions in Romania were included during and after treatment, following a cross-sectional design. PROMs used were SF-36, EQ-5D-5L, WPAI and the app-based audiometry screening tool 'uHear.' Descriptive statistics and relevant statistical tests were used to compare groups between themselves and with the general Romanian population.
RESULTS: Both patients with drug-susceptible and drug-resistant TB experience, with drug-resistant patients experiencing statistically significantly more pain and hearing loss. PROMs show some improvement in the after-treatment group; however, compared with the general Romanian population for which data were available, all groups scored lower on all outcome measures.
CONCLUSION: PROMs offer the possibility of obtaining a more comprehensive view of patients' status, by involving them directly in the medical process and could guide a rehabilitation strategy.

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PMID: 38794852 [Indexed for MEDLINE]

43. Case Report: Multiple Metastatic Primary Multidrug-Resistant Tubercular Abscesses.

Am J Trop Med Hyg. 2024 Jul 9:tpmd230514. doi: 10.4269/ajtmh.23-0514. Online ahead of print.

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This case report presents an atypical manifestation of tuberculosis in a 21-year-old male who presented with multiple subcutaneous swellings in the bilateral heel, left elbow, and base of the left third finger for the previous 6 months. The patient also experienced loss of appetite and unintentional weight loss. Despite initial suspicion of bacterial abscesses, antibiotics did not lead to significant improvement. Further investigations revealed an elevated erythrocyte sedimentation rate and findings suggestive of osteomyelitis on imaging. Gene Xpert testing confirmed multidrug-resistant Mycobacterium tuberculosis as the causative agent. The patient was prescribed a bedaquiline-based multidrug-resistant tuberculosis regimen, which resulted in reduction in swelling size. This report highlights the challenges in diagnosing and managing complex cases of primary multiple tubercular abscesses, especially with drug-resistant strains, emphasizing the importance of timely diagnosis and multidisciplinary management for successful outcomes.

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PMID: 38981508

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

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OBJECTIVE: To assess the efficacy and safety of Bufei Jiedu (BFJD) ranules as adjuvant therapy for patients with multidrug-resistant pulmonary tuberculosis (MDR-PTB).
METHODS: A large-scale, multi-center, double-blinded, and randomized controlled trial was conducted in 18 sentinel hospitals in China from December 2012 to December 2016. A total of 312 MDR-PTB patients were randomly assigned to BFJD Granules or placebo groups (1:1) using a stratified randomization method, which both received the long-course chemotherapy regimen for 18 months (6 Am-Lfx-P-Z-Pto, 12 Lfx-P-Z-Pto). Meanwhile, patients in both groups also received BFJD Granules or placebo twice a day for a total of 18 months, respectively. The primary outcome was cure rate. The secondary outcomes included time to sputum-culture conversion, changes in lung cavities and quality of life (QoL) of patients. Adverse reactions were monitored during and after the trial.
RESULTS: A total of 216 cases completed the trial, 111 in the BFJD Granules group and 105 in the placebo group. BFJD Granules, as an adjuvant treatment, increased the cure rate by 13.6% at the end of treatment, compared with the placebo (58.4% vs. 44.8%, P=0.02), and accelerated the median time to sputum-culture conversion (5 months vs. 11 months). The cavity closure rate of the BFJD Granules group (50.6%, 43/85) was higher than that of the placebo group (32.1%, 26/81; P=0.02) in patients who completed the treatment. At the end of the intensive treatment, according to the 36-item Short Form, the BFJD Granules significantly improved physical functioning, general health, and vitality of patients relative to the placebo group (all P<0.01). Overall, the death rates in the two groups were not significantly different; 5.1% (8/156) in the BFJD Granules group and 2.6% (4/156) in the placebo group.
CONCLUSIONS: Supplementing BFJD Granules with the long-course chemotherapy regimen significantly increased the cure rate and cavity closure rates, and rapidly improved QoL of patients with MDR-PTB (Registration No. ChiCTR-TRC-12002850).

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PMID: 38733454 [Indexed for MEDLINE]

45. [Clinical analysis of adverse reactions in patients with multidrug-resistant and rifampicin-resistant pulmonary tuberculosis treated with delamanid-containing regimen].

Zhonghua Jie He He Hu Xi Za Zhi. 2024 Jul 12;47(7):638-646. doi: 10.3760/cma.j.cn112147-20240229-00117.

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

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Objective: To explore the characteristics of adverse drug reactions during the 24-week therapy with delamanid-containing regimen for patients with multidrug-resistant and rifampicin-resistant pulmonary tuberculosis (MDR/RR-PTB). Methods: The prospective multicenter study was conducted from June 2020 to June 2023. A total of 608 eligible patients with MDR/RR-PTB were enrolled in 26 tuberculosis medical institutions in China including 364 males and 79 females, aged 39.6(19.0-68.0) years. Patients were treated with chemotherapy regimens containing delamanid. Patients were closely supervised during treatment of medication, and all adverse reactions occurring during treatment were monitored and recorded. The clinical characteristics of adverse reactions were evaluated by descriptive analysis. Chi-square test and multivariate logistic regression were used to analyze the related factors of QTcF interval prolongation (QT corrected with Fridericia's formula). Results: Of the 608 patients enrolled in this study, 325 patients (53.5%) reported 710 adverse events within 24 weeks of treatment. The top 6 most common complications were hematological abnormalities (143 patients, 23.5%), QT prolongation (114 patients, 18.8%), liver toxicity (85 patients, 14.0%), gastrointestinal reaction (41 patients, 6.7%), peripheral neuropathy (25 patients, 4.1%) and mental disorders (21 patients, 3.5%). The prolongation of QT interval mostly occurred in the 12th week after the first dose of medication. Serious adverse reactions occurred in 21 patients (3.5%). There were 7 patients (1.2%) with mental disorders, including 2 patients (0.3%) with severe mental disorders. Conclusions: The safety of dalamanid-based regimen in the staged treatment of MDR/RR-PTB patients was generally good, and the incidence of adverse reactions was similar to that reported in foreign studies. This study found that the incidence of QT interval prolongation in Chinese patients was higher than that reported overseas, suggesting that the monitoring of electrocardiogram should be strengthened when using drugs containing delamanid that may cause QT interval prolongation.

Publisher: 目的： 探讨含德拉马尼方案治疗耐多药和利福平耐药肺结核（MDR/RR-PTB）患者24周治疗过程中药物不良反应发生的特点。 方法：

前瞻性多中心研究。2020年6月至2023年6月，在全国26家结核病医疗机构纳入符合条件的MDR/RR-PTB患者608例，其中男364例，女244例，年龄39.6（19.0~68.0）岁。给予含德拉马尼的化疗方案进行治疗，全程密切督导患者服药，监测并记录治疗过程中发生的所有不良反应，通过描述性分析评价不良反应发生的临床特点，用$\chi 2$检验及多因素logistic回归分析QTcF（采用Fridericia公式校正的QT值）间期延长的相关影响因素。

结果：

纳入本研究的608例患者在24周治疗期间内共有325例（53.5%）报告了710例次不良反应。发生频率最高的前6位依次是血液系统损害（143例，23.5%）、心电图QT间期延长（114例，18.8%）、肝毒性（85例，14.0%）、胃肠道反应（41例，6.7%）、周围神经病（25例，4.1%）、精神障碍（21例，3.5%）。心电图QT间期延长大多发生在距首次服药的第12周，其中严重不良反应21例（3.5%）。精神障碍患者7例（1.2%），其中严重精神障碍者有2例（0.3%）。

结论：

含德拉马尼方案阶段性治疗MDR/RR-PTB患者的安全性总体良好，不良反应发生率与国外研究相当。研究发现我国患者人群中QT间期延长的发生率高于国外的相关报道，提示在使用含德拉马尼等可能引起QT间期延长的药物时要加强心电图的监测。.

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46. Identification of potent indolizine derivatives against Mycobacterial tuberculosis: In vitro anti-TB properties, in silico target validation, molecular docking and dynamics studies.

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In the current study, two sets of compounds:
(E)-1-(2-(4-substitutedphenyl)-2-oxoethyl)-4-((hydroxyimino)methyl)pyridinium derivatives (3a-3e); and
(E)-3-(substitutedbenzoyl)-7-((hydroxyimino)methyl)-2-substitutedindolizine-1-carboxylate derivatives (5a-5j), were synthesized and biologically evaluated against two strains of Mycobacterial tuberculosis (ATCC 25177) and multi-drug resistant (MDR) strains. Further, they were also tested in vitro against the mycobacterial

InhA enzyme. The in vitro results showed excellent inhibitory activities against both MTB strains and compounds 5a-5j were found to be more potent, and their MIC values ranged from 5 to 16 μg/mL and 16-64 μg/mL against the M. tuberculosis (ATCC 25177) and MDR-TB strains, respectively. Compound 5h with phenyl and 4-fluorobenzoyl groups attached to the 2- and 3-position of the indolizine core was found to be the most active against both strains with MIC values of 5 μg/mL and 16 μg/mL, respectively. On the other hand, the two sets of compounds showed weak to moderate inhibition of InhA enzyme activity that ranged from 5 to 17 % and 10-52 %, respectively, with compound 5f containing 4-fluoro benzoyl group attached to the 3-position of the indolizine core being the most active (52 % inhibition of InhA). Unfortunately, there was no clear correlation between the InhA inhibitory activity and MIC values of the tested compounds, indicating the probability that they might have different modes of action other than InhA inhibition. Therefore, a computational investigation was conducted by employing molecular docking to identify their putative drug target(s) and, consequently, understand their mechanism of action. A panel of 20 essential mycobacterial enzymes was investigated, of which β-ketoacyl acyl carrier protein synthase I (KasA) and pyridoxal-5'-phosphate (PLP)-dependent aminotransferase (BioA) enzymes were revealed as putative targets for compounds 3a-3e and 5a-5j, respectively. Moreover, in silico ADMET predictions showed adequate properties for these compounds, making them promising leads worthy of further optimization.

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Conflict of interest statement: Declaration of competing interest Authors declare that they have no competing interest.

47. [Tuberculosis among Ukrainian Refugees in Germany - A Comparison of Screening and Reporting Data].

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Since the onset of the war in Ukraine until November 2022, nearly 1 million people sought refuge in Germany. Despite efforts to reduce tuberculosis (TB) cases, Ukraine had a high TB incidence in 2020, with increased rates of multidrug-resistant TB. Conflict and war have historically been associated with TB spread due to delays in diagnosis, treatment interruptions, and increased transmission risks. The World Health Organization (WHO) estimated a rise in TB cases in the EU region due to refugee movements. In Germany, screening methods used in testing individuals in communal housing involving chest X-rays or immunological tests were variable. A survey conducted by the DZK within the nationwide TB working group evaluated TB screening methods and results for Ukrainian refugees. Out of 26,196 individuals aged over 15, 48 TB cases were detected, with a higher-than-expected incidence. About 42% of cases were multidrug-resistant TB. The screening findings differed from both the WHO's estimates as well as TB cases reported to the Robert Koch Institut (RKI) in 2022. A preliminary comparison of the numbers is presented here. The differing results emphasize the need for ongoing data collection and analysis to adapt resources and interventions to the evolving TB situation among Ukrainian refugees in Germany, especially considering the ongoing conflict and potential for increased TB cases in the future.

Publisher: Seit Beginn des Krieges in der Ukraine bis November 2022 haben fast 1 Million Menschen Zuflucht in Deutschland gefunden. Trotz der Bemühungen, die Tuberkulose (TB)-Fallzahlen zu senken, verzeichnete die Ukraine im Jahr 2020 eine hohe TB-Inzidenz, insbesondere mit hohen Raten multiresistenter TB. Konflikte und Kriege werden aufgrund von Verzögerungen bei der Diagnose, Behandlungsunterbrechungen und erhöhten Ansteckungsrisiken mit der Ausbreitung von TB in Verbindung gebracht. Schätzungen der Weltgesundheitsorganisation (WHO) gingen aufgrund der Flüchtlingsbewegungen von einem Anstieg der TB-Zahlen in der EU-Region aus. In Deutschland gibt es unterschiedliche Screening-Methoden für Personen in Gemeinschaftsunterkünften, darunter Röntgenaufnahmen des Thorax oder immunologische Tests. Eine im Arbeitskreis Tuberkulose des BVÖGD durch das DZK durchgeführte Umfrage untersuchte die Methoden und Ergebnisse des TB-Screenings für ukrainische Geflüchtete. Unter insgesamt 26 196 untersuchten Personen über 15 Jahren wurden 48 TB-Fälle entdeckt. Bei etwa 42% der Fälle handelte es sich um eine multiresistente TB. Die Screening-Ergebnisse weichen sowohl von den Schätzungen der WHO als auch von den im Jahr 2022 an das Robert-Koch-Institut (RKI) gemeldeten TB-Fällen ab. Hier wird ein orientierender Vergleich der Zahlen dargestellt. Die abweichenden Ergebnisse unterstreichen die Notwendigkeit einer kontinuierlichen Datenerhebung und -analyse, um Ressourcen und Interventionen an die sich entwickelnde TB-Situation unter ukrainischen Geflüchteten in Deutschland anzupassen, insbesondere angesichts des anhaltenden Konflikts und der Möglichkeit einer künftigen Zunahme von TB-Fällen.

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48. Pharmacokinetic-pharmacodynamic modeling of tuberculosis time to positivity and colony-forming unit to assess the response to dose-ranging linezolid.

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According to the World Health Organization, the number of tuberculosis (TB) infections and the drug-resistant burden worldwide increased by 4.5% and 3.0%, respectively, between 2020 and 2021. Disease severity and complexity drive the interest for undertaking new clinical trials to provide efficient treatment to limit spread and drug resistance. TB Alliance conducted a phase 2 study in 106 patients to guide linezolid (LZD) dose selection using early bactericidal activity over 14 days of treatment. LZD is highly efficient for drug-resistant TB treatment, but treatment monitoring is required since serious adverse events can occur. The objective of this study was to develop a pharmacokinetic-pharmacodynamic (PKPD) model to analyze the dose-response relationship between linezolid exposure and efficacy biomarkers. Using time to positivity (TTP) and colony-forming unit (CFU) count data, we developed a PKPD model in six dosing regimens, differing on LZD dosing intensity. A one-compartment model with five transit absorption compartments and non-linear auto-inhibition elimination described best LZD pharmacokinetic characteristics. TTP and CFU logarithmic scaled [log(CFU)] showed a bactericidal activity of LZD against Mycobacterium tuberculosis. TTP was defined by a model with two significant covariates: the presence of uni- and bilateral cavities decreased baseline TTP value by 24%, and an increase on every 500 mg/L/h of cumulative

area under the curve increased the rate at which TTP and CFU change from baseline by 20% and 11%, respectively.
CLINICAL TRIALS: This study is registered with ClinicalTrials.gov as NCT02279875.

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PMID: 39016594

49. Clofazimine pulmonary crystal deposition syndrome: a case of pseudo haemoptysis.

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Clofazimine is an antimycobacterial, anti-inflammatory agent used in the management of leprosy and multidrug-resistant (MDR) tuberculosis. It has high oral bioavailability and poor solubility because of which prolonged administration of the drug results in its accumulation as intracellular biocrystals in tissue macrophages. We describe the case of a female patient in her early 30s who was on therapy for MDR tuberculosis. She presented with streaky haemoptysis of 6 months. Radiographic examination showed no abnormality in pulmonary vasculature and parenchyma. Bronchoscopy showed diffuse red-coloured flecks in tracheal and bronchial mucosa. The retrieved bronchoalveolar lavage (BAL) fluid was reddish-purple in colour. Microscopic examination of BAL fluid showed reddish clofazimine crystal deposition in alveolar macrophages. Serum and BAL clofazimine levels were performed using high performance liquid chromatography which confirmed high drug levels. She developed reddish discolouration of the skin during therapy due to clofazimine deposition. A diagnosis of pulmonary clofazimine crystal deposition syndrome causing pseudohaemoptysis was established.

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News Articles

1. **Relief in South Africa after J&J reversal allows key tuberculosis drug production at lower prices**

   https://abcnews.go.com/Health/wireStory/south-africa-drops-probe-jj-after-agrees-lower-111771629

   Johnson and Johnson successfully applied for a patent extension on bedaquiline; however, in a big win for LMI countries, the company has decided not to enforce its patent, allowing generic producers to manufacture the drug. Additionally, J&J has reduced the price of bedaquiline for South Africa by around 40%, making it more affordable for the country. J&J's reversal of its past decisions regarding bedaquiline was prompted by an investigation of the company's pricing policies led by the South African government.
2. **Scientists identify 'unconventional' new pathway for TB vaccines**

   https://medicalxpress.com/news/2024-07-scientists-unconventional-pathway-tb-vaccines.html

   Researchers have identified a B cell pathway to target with future TB vaccines using antibody-independent mechanisms. They found that MZB cells are upregulated during TB infection and are linked to cell-mediated immunity after an infection. This pathway opens up a new strategy for TB vaccine development that does not rely upon antibody creation.
3. **FDA Grants Traditional Approval to TB Treatment Sirturo**

   https://www.empr.com/home/news/fda-grants-traditional-approval-to-tb-treatment-sirturo/?cmid=ccec881d-62b3-4133-88e1-0dc9f2f1a08c

   The FDA has granted traditional approval for Sirturo in pediatric and adult populations based on the results of the STREAM study. The STREAM study was a phase 3 clinical trial that compared standard-of-care lines of treatment to Sirturo for MDR-TB. The trial showed 82.7% of patients responded well to Sirturo compared to 71.1% for the SOC group.