# January Literature

1**. PPD Skin Test.**

Pahal P, Sharma S(1).

In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan–.
2021 Feb 4.

Tuberculosis remains a major public health concern and a leading cause of morbidity and mortality worldwide, especially in developing countries. Tuberculosis is a fatal bacterial infection caused by the bacterium Mycobacterium tuberculosis, a highly contagious droplet infection, which primarily affects the lungs. However, it can affect any area of the body, which includes bones, joints, central nervous system, etc. The treatment for tuberculosis is available and is effective. Although the overall incidence and prevalence of tuberculosis have been declining, the incidence of multidrug-resistant tuberculosis is steadily rising. The Asians and Hispanics account for more than half of the new tuberculosis cases, with the highest incidence in India, China, Indonesia, Pakistan, Nigeria, and South Africa. However, in the United States, recent trends show a significant decline in this infection.[1] Active and Latent TB Infection  A person with active infection usually presents with symptoms of the part affected and constitutional symptoms such as unexplained weight loss, fever, fatigue, loss of appetite, and night sweats. The latent TB, however, is asymptomatic and non-infectious. Early diagnosis of active TB is crucial to managing the disease in time and prevent its spread. The latent TB infection is non-infectious and asymptomatic, with a significant worldwide prevalence (33%). Since this population carries a risk of reactivation in immunocompromised states and progress to an active TB disease, which is symptomatic and highly contagious, latent TB is an important public health issue. The LTBI progression risk to active disease is maximum in the first two years after exposure. The progression, detection, and treatment of latent TB cases are important for tuberculosis control and reduce the disease burden. The LTBI progression risk declines with age as the immunity increases with age. The risk of progression in infants is 50%, which declines to 1% to 2% by the age of 10 years. TB Screening Tests Two screening tests can demonstrate TB infection: PPD Skin test (Mantoux test/tuberculin skin test). IGRA (interferon-gamma release assay). Both these tests evaluate cell-mediated immunity, which usually occurs when the person has been exposed to TB bacteria. The skin reaction is the response mediated by T lymphocytes (cell-mediated immunity). The positivity of these tests, however, does not distinguish between latent or active tuberculosis. Therefore, symptom assessment and further testing

(chest radiograph, sputum test for acid-fast bacillus, CT scan) and are essential to look for an active infection. There is no definitive test to diagnose LTBI, which is a clinical diagnosis. The diagnosis of LTBI is done based on a history of prior TB infection and ruling out active TB disease. PPD Skin Test/ Tuberculosis Skin Test Purified protein derivative test (PPD skin test), administered through the Mantoux technique, is a type IV hypersensitivity skin reaction to 'tuberculin.' Therefore, also known as the tuberculin skin test (TST skin test) and Mantoux test. This test was developed by Koch and further developed by Charles Mantoux, who described the intradermal technique in 1912. Tuberculin protein used in the test is extracted from mycobacterium tuberculosis cultures and is used as a purified protein derivative. However, a standardized PPD-S is used, which is a tuberculous mycobacterium (non-tuberculous Mycobacterium are identified by a letter other than S). The results of this test are interpreted by measuring the hypersensitivity reaction (delayed-type hypersensitivity) to tuberculin purified protein derivative, derived from Mycobacterium tuberculosis. The peak of the induration reaction occurs after 24 hours of the test injection. Induration of the skin at the injection site occurs secondary to cell infiltration. It takes about 6 to 8 weeks after exposure to the bacteria for the PPD test to be positive. Two visits are required in this test. First visit to get the test administered, and the second visit to get the reading of the test after 48 to 72 hours of test placement.



PMID: 32310497

2. **[Treatment of drug-resistant tuberculosis in adults and children. A narrative review].**

Medicina (B Aires). 2022;82(1):117-129.

Palmero DJ(1)(2), Lagrutta L(3)(2), Inwentarz SJ(2), Vescovo M(3)(2), Aidar OJ(3)(2), González Montaner PJ(3)(2).

Since 2018, important changes in the treatment of drug-resistant tuberculosis have been produced in the light of new evidence. The discovery of new anti-tuberculosis drugs, such as bedaquiline and nitroimidazopirane derivatives, as well as the use of repurposed drugs, led to international organizations to recommend new, totally oral, treatment regimens for mono-resistant and multidrug-resistant tuberculosis, leaving aside the prolonged use of injectables, with their inherent toxicity and discomfort. Some definitions of drug-resistant tuberculosis have changed. The duration of treatment is also under review, leading some new regimens under study, such as BPaL (bedaquiline,

pretomanid and linezolid), to a duration similar to that for treating susceptible tuberculosis. In this narrative review, we describe the new definitions, some basic diagnostic aspects, the pharmacological aspects, and the new classification of drugs to be used in the treatment of drug-resistant tuberculosis as well as the currently proposed schemes to treat it available within the Argentinean context. Finally, we include a brief review of ongoing clinical trials on new shortened treatments.

PMID: 35037870 [Indexed for MEDLINE]

3. **Confronting and Coping with Multidrug-Resistant Tuberculosis: Life Experiences in Thailand.**

Qual Health Res. 2022 Jan;32(1):159-167. doi: 10.1177/10497323211049777. Epub 2021 Nov 30.

Numpong S(1), Kengganpanich M(2), Kaewkungwal J(1), Pan-Ngum W(1), Silachamroon U(3), Kasetjaroen Y(4), Lawpoolsri S(1).

In this article, we aimed to understand the life experiences of Thai persons diagnosed with multi-drug-resistant tuberculosis (MDR-TB). A qualitative study using a face-to-face in-depth interview was conducted at a hospital in Thailand which has the highest prevalence of MDR-TB in the country between January and February 2019. Twenty persons living with MDR-TB in Thailand were purposively selected to represent a variety of experiences based on different gender, ages, and treatment phases. Qualitative data were transcribed and thematic analysis was applied to identify common themes and sub-themes. The results indicated that all participants faced emotional difficulties, such as fear of death, fear of stigmatization, confusion, and sadness when first knowing of their diagnosis. Family and social support were the main ways that the patients coped with difficult situations. Suicidal ideas were more prevalent among patients with poor family support. Screening for mental health problems should be routinely performed in MDR-TB patients. Proper health education should be provided to patients and families to reduce emotional difficulties and stigmatization.

DOI: 10.1177/10497323211049777
PMCID: PMC8739603
PMID: 34845946 [Indexed for MEDLINE]

4. **Anti-tuberculosis drug resistance in Slovakia, 2018-2019: The first whole-genome epidemiological study.**

J Clin Tuberc Other Mycobact Dis. 2021 Dec 20;26:100292. doi: 10.1016/j.jctube.2021.100292. eCollection 2022 Feb.

Dohál M(1), Dvořáková V(2), Šperková M(2), Porvazník I(3)(4), Cabibbe AM(5), Trovato A(5), Spitaleri A(5), Rasmussen EM(6), Pršo K(1), Škereňová M(7), Cirillo DM(5), Solovič I(3), Mokrý J(1).

OBJECTIVE: The resistance of Mycobacterium (M.) tuberculosis to antituberculosis drugs poses a major threat to global public health. Whole genome sequencing (WGS) is an increasingly preferred method in the diagnostics and monitoring of the transmission dynamics of resistant forms of tuberculosis (TB). The aim of the study was to, for the first time, use the sequencing-based analysis to study the transmission and resistance patterns of a systematic and recent collection of extensively drug resistant (XDR) and multidrug resistant tuberculosis (MDR-TB) isolates and to expand our knowledge about drug resistant (DR) TB epidemiological dynamics in Slovakia.
DESIGN: A total of 495 patients with pulmonary TB, who were referred to National Reference Laboratory for Mycobacteriology (Vyšné Hágy, Slovakia) in the years 2018-2019, were studied. Out of the total of 495 patients, 4 XDR-TB (0.8%) and 8 (1.6%) MDR-TB isolates were identified by conventional drug susceptibility testing on Löwenstein-Jensen solid medium and subjected to whole genome sequencing. Sequencing data were evaluated for molecular-epidemiological analysis and identification of resistance patterns.
RESULTS: Phylogenetic and cluster analysis showed extensive recent transmission events and the predominance of Euro-American lineage 4.7 in Slovakia. However, phylogenetic analysis revealed the circulation of several lineages that originally occurred in Eastern European countries. Resistance patterns for first- and second-line antituberculosis drugs characterized by whole genome sequencing were in high concordance with the results of phenotypic drug susceptibility testing.
CONCLUSION: Forty percent of at least MDR-TB isolates were not genetically linked, indicating that appropriate measures should be taken to monitor and prevent the spread of drug-resistant tuberculosis within the country as well as in other regions.



DOI: 10.1016/j.jctube.2021.100292
PMCID: PMC8717600
PMID: 35005254

5. **Budgetary impact of using BPaL for treating extensively drug-resistant tuberculosis.**

BMJ Glob Health. 2022 Jan;7(1):e007182. doi: 10.1136/bmjgh-2021-007182.

Mulder C(1)(2), Rupert S(2), Setiawan E(3), Mambetova E(4), Edo P(5), Sugiharto J(6), Useni S(5), Malhotra S(7)(8), Cook-Scalise S(7)(9), Pambudi I(10), Kadyrov A(11), Lawanson A(12), van den Hof S(13)(14), Gebhard A(13), Juneja S(7), Sohn H(15).

INTRODUCTION: Bedaquiline, pretomanid and linezolid (BPaL) is a new all oral, 6-month regimen comprised of bedaquiline, the new drug pretomanid and linezolid, endorsed by the WHO for use under operational research conditions in patients with extensively drug-resistant tuberculosis (XDR-TB). We quantified per-patient treatment costs and the 5-year budgetary impact of introducing BPaL in Indonesia, Kyrgyzstan and Nigeria.
METHODS: Per-patient treatment cost of BPaL regimen was compared head-to-head with the conventional XDR-TB treatment regimen for respective countries based on cost estimates primarily assessed using microcosting method and expected frequency of each TB service. The 5-year budget impact of gradual introduction of BPaL against the status quo was assessed using a Markov model that represented patient's treatment management and outcome pathways.
RESULTS: The cost per patient completing treatment with BPaL was US$7142 in Indonesia, US$4782 in Kyrgyzstan and US$7152 in Nigeria - 57%, 78% and 68% lower than the conventional regimens in the respective countries. A gradual adoption of the BPaL regimen over 5 years would result in an 5-year average national TB service budget reduction of 17% (US$128 780) in XDR-TB treatment-related expenditure in Indonesia, 15% (US$700 247) in Kyrgyzstan and 32% (US$1 543 047) in Nigeria.
CONCLUSION: Our study demonstrates that the BPaL regimen can be highly cost-saving compared with the conventional regimens to treat patients with XDR-TB in high drug-resistant TB burden settings. This supports the rapid adoption of the BPaL regimen to address the significant programmatic and clinical challenges in managing patients with XDR-TB in high DR-TB burden countries.



DOI: 10.1136/bmjgh-2021-007182
PMID: 34992077

6. **Multidrug-resistant Tuberculosis in U.S.-bound Immigrants and Refugees.**

Ann Am Thorac Soc. 2021 Dec 23. doi: 10.1513/AnnalsATS.202105-580OC. Online

ahead of print.

Liu Y(1), Posey DL(2), Yang Q(3), Weinberg MS(2), Maloney SA(4), Lambert LA(5), Ortega LS(6), Marano N(2), Cetron MS(2), Phares CR(2).

RATIONALE: Approximately two-thirds of new cases of tuberculosis (TB) in the United States are among non-U.S.-born persons. Culture-based overseas TB screening in U.S.-bound immigrants and refugees has substantially reduced the importation of TB into the United States, but it is unclear to what extent this program prevents the importation of multidrug-resistant TB (MDR-TB).
OBJECTIVES: To study the epidemiology of MDR-TB in U.S.-bound immigrants and refugees, and to evaluate effect of culture-based overseas TB screening in U.S.-bound immigrants and refugees on reducing the importation of MDR-TB into the United States.
METHODS: We analyzed data of immigrants and refugees who completed overseas treatment for culture-positive TB during 2015-2019. We also compared mean annual number of MDR-TB cases in non-U.S.-born persons within 1 year of arrival in the United States between 1996-2006 (when overseas screening followed a smear-based algorithm) and 2014-2019 (after full implementation of a culture-based algorithm).
RESULTS: Of 3,300 culture-positive TB cases prevented by culture-based overseas TB screening in immigrants and refugees during 2015-2019, 122 (3.7%, 95% confidence interval (CI) 3.1-4.1) had MDR-TB, 20 (0.6%, 95% CI 0.3-0.9) had rifampicin-resistant TB, 382 (11.6%, 95% CI 10.5-12.7) had isoniazid-resistant TB, and 2,776 (84.1%, 95% CI 82.9-85.4) had rifampicin- and isoniazid-susceptible TB. None were diagnosed with extensively drug-resistant TB (XDR-TB). Culture-based overseas TB screening in U.S.-bound immigrants and refugees prevented 24.4 MDR-TB cases per year from arriving in the United States, 18.2 cases more than smear-based overseas TB screening. Mean annual number of MDR-TB cases among non-U.S.-born persons within 1 year of arrival in the United States decreased from 34.6 cases in 1996-2006 to 19.5 cases in 2014-2019 (difference of 15.1, $p<0.001$).
CONCLUSIONS: Culture-based overseas TB screening in U.S.-bound immigrants and refugees substantially reduced the importation of MDR-TB into the United States.

DOI: 10.1513/AnnalsATS.202105-580OC
PMID: 34941475

7. **Bedaquiline Drug Resistance Emergence Assessment in Multidrug-Resistant Tuberculosis (MDR-TB): a 5-Year Prospective In Vitro Surveillance Study of Bedaquiline and Other Second-Line Drug Susceptibility Testing in MDR-TB Isolates.**

J Clin Microbiol. 2022 Jan 19;60(1):e0291920. doi: 10.1128/JCM.02919-20. Epub 2021 Oct 27.

Kaniga K(1), Hasan R(2)(3), Jou R(4), Vasiliauskienė E(5), Chuchottaworn C(6), Ismail N(7), Metchock B(8), Miliauskas S(9), Viet Nhung N(10), Rodrigues C(11), Shin S(12), Simsek H(13)(14), Smithtikarn S(15), Ngoc ALT(10), Boonyasopun J(16), Kazi M(11), Kim S(12), Kamolwat P(15), Musteikiene G(9), Sacopon CA(17), Tahseen S(18), Vasiliauskaitė L(5), Wu MH(4), Vally Omar S(7).

Bedaquiline Drug Resistance Emergence Assessment in Multidrug-resistant tuberculosis (MDR-TB) (DREAM) was a 5-year (2015 to 2019) phenotypic drug resistance surveillance study across 11 countries. DREAM assessed the susceptibility of 5,036 MDR-TB isolates of bedaquiline treatment-naive patients to bedaquiline and other antituberculosis drugs by the 7H9 broth microdilution (BMD) and 7H10/7H11 agar dilution (AD) MIC methods. Bedaquiline AD MIC quality control (QC) range for the H37Rv reference strain was unchanged, but the BMD MIC QC range (0.015 to 0.12 μg/ml) was adjusted compared with ranges from a multilaboratory, multicountry reproducibility study conforming to Clinical and Laboratory Standards Institute Tier-2 criteria. Epidemiological cutoff values of 0.12 μg/ml by BMD and 0.25 μg/ml by AD were consistent with previous bedaquiline breakpoints. An area of technical uncertainty or intermediate category was set at 0.25 μg/ml and 0.5 μg/ml for BMD and AD, respectively. When applied to the 5,036 MDR-TB isolates, bedaquiline-susceptible, -intermediate, and -resistant rates were 97.9%, 1.5%, and 0.6%, respectively, for BMD and 98.8%, 0.8%, and 0.4% for AD. Resistance rates were the following: 35.1% ofloxacin, 34.2% levofloxacin, 33.3% moxifloxacin, 1.5% linezolid, and 2% clofazimine. Phenotypic cross-resistance between bedaquiline and clofazimine was 0.4% in MDR-TB and 1% in pre-extensively drug-resistant (pre-XDR-TB)/XDR-TB populations. Coresistance to bedaquiline and linezolid and clofazimine and linezolid were 0.1% and 0.3%, respectively, in MDR-TB and 0.2% and 0.4%, respectively, in pre-XDR-TB/XDR-TB populations. Resistance rates to bedaquiline appear to be low in the bedaquiline-treatment-naive population. No treatment-limiting patterns for cross-resistance and coresistance have been identified with key TB drugs to date.

DOI: 10.1128/JCM.02919-20
PMID: 34705538

8. **Genetic Diversity and Transmission of Multidrug-Resistant Mycobacterium tuberculosis strains in Lusaka, Zambia.**

Int J Infect Dis. 2022 Jan;114:142-150. doi: 10.1016/j.ijid.2021.10.044. Epub 2021 Oct 27.

Chizimu JY(1), Solo ES(2), Bwalya P(2), Kapalamula TF(3), Akapelwa ML(3), Lungu P(4), Shrestha D(5), Fukushima Y(3), Mukonka V(6), Thapa J(3), Nakajima C(7), Suzuki Y(8).

OBJECTIVE: Zambia is among the 30 high tuberculosis burden countries in the world. Despite increasing reports of multidrug-resistant tuberculosis (MDR-TB) in routine surveillance, information on the transmission of MDR Mycobacterium tuberculosis strains is largely unknown. This study elucidated the genetic diversity and transmission of MDR M. tuberculosis strains in Lusaka, Zambia.
METHODS: Eighty-five MDR M. tuberculosis samples collected from 2013 to 2017 at the University Teaching Hospital were used. Drug-resistance associated gene sequencing, spoligotyping, 24-loci mycobacterial interspersed repetitive units-variable number of tandem repeats (MIRU-VNTR), and multiplex PCR for RD-Rio sub-lineage identification were applied.
RESULTS: The identified clades were LAM (48%), CAS (29%), T (14%), X (6%) and Harlem (2%). Strains belonging to SITs 21/CAS1-Kili and 20/LAM1 formed the largest clonal complexes. Combined spoligotyping and 24 loci-MIRU-VNTR revealed 47 genotypic patterns with a clustering rate of 63%. Ninety-five percent of LAM strains belonged to the RD-Rio sub-lineage.
CONCLUSION: The high clustering rate suggested that a large proportion of MDR-TB was due to recent transmission rather than the independent acquisition of MDR. This spread was attributed to clonal expansion of SIT21/CAS1-Kili and SIT20/LAM1 strains. Therefore, TB control programs recommending genotyping coupled with conventional epidemiological methods can guide measures for stopping the spread of MDR-TB.



DOI: 10.1016/j.ijid.2021.10.044
PMID: 34718155 [Indexed for MEDLINE]

9. **Tuberculosis drug discovery: Progression and future interventions in the wake of emerging resistance.**

Eur J Med Chem. 2021 Dec 26;229:114066. doi: 10.1016/j.ejmech.2021.114066. Online ahead of print.

Perveen S(1), Kumari D(1), Singh K(1), Sharma R(2).

The emergence of drug resistance continues to afflict TB control where drug resistant strains have become a global health concern. Contrary to drug-sensitive TB, the treatment of MDR/XDR-TB is more complicated requiring the

administration of second-line drugs that are inefficient than the first line drugs and are associated with greater side effects. The emergence of drug resistant Mtb strains had coincided with an innovation void in the field of drug discovery of anti-mycobacterials. However, the approval of bedaquiline and delamanid recently for use in MDR/XDR-TB has given an impetus to the TB drug discovery. The review discusses the drug discovery efforts in the field of tuberculosis with a focus on the strategies adopted and challenges confronted by TB research community. Here, we discuss the diverse clinical candidates in the current TB drug discovery pipeline. There is an urgent need to combat the current TB menace through multidisciplinary approaches and strategies making use of the recent advances in understanding the molecular biology and pathogenesis of Mtb. The review highlights the recent advances in drug discovery, with the host directed therapeutics and nanoparticles-drug delivery coming up as important tools to fight tuberculosis in the future.



DOI: 10.1016/j.ejmech.2021.114066
PMID: 34973508

10. **Epidemiological Characteristics and Risk Factors Related to Drug-resistant Tuberculosis in Luanda, Angola.**

Am J Trop Med Hyg. 2022 Jan 10:tpmd210659. doi: 10.4269/ajtmh.21-0659. Online ahead of print.

Sebastião CS(1)(2)(3), Samulengo J(1), Sacomboio E(1)(3), Francisco NM(1), Teixeira C(1), António S(1), Kinanga M(4), Neto Z(1), Paixão J(1), Mateus A(1), David Z(1), de Vasconcelos JN(1)(2), Morais J(1)(5).

Tuberculosis (TB) is a major cause of illness and public health concern, especially in resource-limited countries. This study analyzed the characteristics related to anti-TB drug resistance. Moreover, we examined the evidence-based indications for the treatment of active TB in Angola. This study evaluated the medical records of 176 patients screened for TB from January to September 2016 in Luanda, the capital city of Angola. Approximately 66.5% of the patients were newly diagnosed with active TB. The residence area showed a significant relationship with TB (P = 0.025), whereas age group (P = 0.272), gender (P = 0.853), and HIV status (P = 0.284) did not showed any relationship with TB. Overall, 72.4% of TB patients had resistance to at least one of the anti-TB drugs. The risk of anti-TB drug resistance was higher in males (odds ratio [OR]: 1.22; 95% confidence interval [CI]: 0.42-3.58, P = 0.685] and in TB-HIV coinfected patients [OR: 1.39; (95% CI: 0.26-7.28), P = 0.700], whereas

it was lower in patients aged 30 years or older (OR: 0.56; 95% CI: 0.18-1.69) P = 0.303) and in patients living in urbanized areas (OR: 0.74; 95% CI: 0.17-3.25; P = 0.685). Our findings showed that drug-resistant TB is emerging in Angola. Further studies on factors related to anti-TB drug resistance are urgently needed to ascertain the magnitude of the problem and to proffer strategies toward TB control in Angola.

DOI: 10.4269/ajtmh.21-0659
PMID: 35008058

11. **Determinants, risk factors and spatial analysis of multi-drug resistant pulmonary tuberculosis in Jodhpur, India.**

Monaldi Arch Chest Dis. 2022 Jan 18. doi: 10.4081/monaldi.2022.2026. Online ahead of print.

Ladha N(1), Bhardwaj P(2), Chauhan NK(3), Kh N(4), Nag VL(5), Giribabu D(6).

This study was planned to estimate the proportion of confirmed multi-drug resistance pulmonary tuberculosis (TB) cases out of the presumptive cases referred to DTC (District Tuberculosis Center) Jodhpur for diagnosis; to identify clinical and socio-demographic risk factors associated with the multidrug-resistant pulmonary TB and to assess the spatial distribution to find out clustering and pattern in the distribution of pulmonary TB with the help of Geographic Information System (GIS). In the Jodhpur district, 150 confirmed pulmonary multi-drug resistant tuberculosis (MDR-TB) cases, diagnosed by probe-based molecular drug susceptibility testing method and categorized as MDR in DTC's register (District Tuberculosis Center), were taken. Simultaneously, 300 control of confirmed non-MDR or drug-sensitive pulmonary TB patients were taken. Statistical analysis was done with logistic regression. In addition, for spatial analysis, secondary data from 2013-17 was analyzed using Global Moran's I and Getis and Ordi (Gi*) statistics. In 2012-18, a total of 12563 CBNAAT (Cartridge-based nucleic acid amplification test) were performed. 2898 (23%) showed M. TB positive but rifampicin sensitive, and 590 (4.7%) showed rifampicin resistant. Independent risk factors for MDR TB were ≤60 years age (AOR 3.0, CI 1.3-7.1); male gender (AOR 3.4, CI 1.8-6.7); overcrowding (AOR 1.6, CI 1.0-2.7); using chulha (smoke appliance) for cooking (AOR 2.5, CI 1.2-4.9), past TB treatment (AOR 5.7, CI 2.9-11.3) and past contact with MDR patient (AOR 10.7, CI 3.7-31.2). All four urban TUs (Tuberculosis Units) had the highest proportion of drug-resistant pulmonary TB. There was no statistically significant clustering, and the pattern of cases was primarily random. Most of the hotspots generated were present near the administrative boundaries of TUs, and the new ones mostly appeared in the area near the previous hotspots. A random pattern seen in

cluster analysis supports the universal drug testing policy of India. Hotspot analysis helps cross administrative border initiatives with targeted active case finding and proper follow-up.

DOI: 10.4081/monaldi.2022.2026
PMID: 35044136

12. **'Practical management of suspected hypersensitivity reactions to anti-tuberculosis drugs.'.**

Clin Exp Allergy. 2021 Dec 22. doi: 10.1111/cea.14084. Online ahead of print.

Bermingham WH(1), Bhogal R(2), Nagarajan S(3), Mutlu L(1), El-Shabrawy RM(4), Madhan R(5), Maheshwari UM(6), Murali M(7), Kudagammana ST(8), Shrestha R(9), Sumantri S(10), Christopher DJ(11), Mahesh PA(12), Dedicoat M(13), Krishna MT(1)(14).

Tuberculosis (TB) is the commonest cause of death by a single infectious agent globally and ranks amongst the top ten causes of global mortality. The incidence of TB is highest in Low-Middle Income countries (LMICs). Prompt institution of, and compliance with, therapy are cornerstones for a favourable outcome in TB and to mitigate the risk of multiple drug resistant (MDR)-TB, which is challenging to treat. There is some evidence that adverse drug reactions (ADRs) and hypersensitivity reactions (HSRs) to anti-TB drugs occur in over 60% and 3-4% of patients respectively. Both ADRs and HSRs represent significant barriers to treatment adherence and are recognised risk factors for MDR-TB. HSRs to anti-TB drugs are usually cutaneous and benign, occur within few weeks after commencement of therapy and are likely to be T-cell mediated. Severe and systemic T-cell mediated HSRs and IgE mediated anaphylaxis to anti-TB drugs are relatively rare, but important to recognise and treat promptly. T-cell mediated HSRs are more frequent amongst patients with co-existing HIV infection. Some patients develop multiple sensitisation to anti-TB drugs. Whilst skin tests, patch tests and in vitro diagnostics have been used in the investigation of HSRs to anti-TB drugs, their predictive value is not established, they are onerous, require specialist input of an allergist and are resource-dependent. This is compounded by the global, unmet demand for allergy specialists, particularly in low income countries (LICs) / LMICs and now the challenging circumstances of the SARS-CoV-2 pandemic. This narrative review provides a critical analysis of the limited published evidence on this topic and proposes a cautious and pragmatic approach to optimise and standardise the management of HSRs to anti-TB drugs. This includes clinical risk stratification and a dual strategy involving sequential re-challenge and rapid drug desensitisation. Furthermore, a concerted international effort is needed to generate real-time data on ADRs, HSRs, safety

and clinical outcomes of these interventions.



DOI: 10.1111/cea.14084
PMID: 34939251

13**. Pretomanid for tuberculosis: a systematic review.**

Clin Microbiol Infect. 2022 Jan;28(1):31-42. doi: 10.1016/j.cmi.2021.08.007. Epub 2021 Aug 14.

Gils T(1), Lynen L(2), de Jong BC(3), Van Deun A(4), Decroo T(5).

BACKGROUND: Outcomes of treatment of tuberculosis patients with regimens including pretomanid have not yet been systematically reviewed.
OBJECTIVES: To appraise existing evidence on efficacy and safety of pretomanid in tuberculosis.
DATA SOURCES: Pubmed, clinicaltrials.gov. and Cochrane library.
STUDY ELIGIBILITY CRITERIA: Quantitative studies presenting original data on clinical efficacy or safety of pretomanid.
PARTICIPANTS: Patients with tuberculosis.
INTERVENTIONS: Treatment with pretomanid or pretomanid-containing regimens in minimum one study group.
METHODS: Two authors independently extracted data and assessed risk of bias. Data on efficacy (early bactericidal activity, bactericidal activity, end-of-treatment outcomes and acquired resistance) and safety were summarized in tables. Mean differences in efficacy outcomes between regimens across studies were calculated.
RESULTS: Eight studies were included; four randomized controlled trials on 2-week early bactericidal activity in rifampicin-susceptible tuberculosis, three trials with randomized rifampicin-susceptible tuberculosis arms and a single rifampicin-resistant tuberculosis arm (two on 8-week bactericidal activity, one on end-of-treatment outcomes), one single-arm trial with end-of-treatment outcomes in highly resistant tuberculosis. Activity of pretomanid-moxifloxacin-pyrazinamide was superior to standard treatment on daily change in colony-forming units at days 0-2, 0-56 and 7-56 and time to culture conversion in rifampicin-susceptible tuberculosis (hazard ratio: 1.7; 95% CI 1.1-2.7), but not at end of treatment in one study. This study was stopped due to serious hepatotoxic adverse events, including three deaths, in 4% (95% CI 2-8) patients on pretomanid-moxifloxacin-pyrazinamide and none in controls. In patients with uncomplicated rifampicin-resistant tuberculosis on pretomanid-moxifloxacin-pyrazinamide treatment, 91% (95% CI 59-100) had

favourable end-of-treatment outcomes. In patients with highly resistant tuberculosis, 90% (95% CI 83-95) on pretomanid-bedaquiline-linezolid had favourable outcomes six months after treatment, but linezolid-related toxicity was frequent. No acquired resistance to pretomanid was reported.
CONCLUSIONS: Evidence suggests an important role for pretomanid in rifampicin-resistant and highly resistant tuberculosis. Trials comparing pretomanid to existing core and companion drugs are needed to further define that role.



DOI: 10.1016/j.cmi.2021.08.007
PMID: 34400340 [Indexed for MEDLINE]

14. **Differentiating between drug-sensitive and drug-resistant tuberculosis with machine learning for clinical and radiological features.**

Quant Imaging Med Surg. 2022 Jan;12(1):675-687. doi: 10.21037/qims-21-290.

Yang F(1), Yu H(1), Kantipudi K(2), Karki M(1), Kassim YM(1), Rosenthal A(2), Hurt DE(2), Yaniv Z(2), Jaeger S(1).

BACKGROUND: Tuberculosis (TB) drug resistance is a worldwide public health problem that threatens progress made in TB care and control. Early detection of drug resistance is important for disease control, with discrimination between drug-resistant TB (DR-TB) and drug-sensitive TB (DS-TB) still being an open problem. The objective of this work is to investigate the relevance of readily available clinical data and data derived from chest X-rays (CXRs) in DR-TB prediction and to investigate the possibility of applying machine learning techniques to selected clinical and radiological features for discrimination between DR-TB and DS-TB. We hypothesize that the number of sextants affected by abnormalities such as nodule, cavity, collapse and infiltrate may serve as a radiological feature for DR-TB identification, and that both clinical and radiological features are important factors for machine classification of DR-TB and DS-TB.
METHODS: We use data from the NIAID TB Portals program (https://tbportals.niaid.nih.gov), 1,455 DR-TB cases and 782 DS-TB cases from 11 countries. We first select three clinical features and 26 radiological features from the dataset. Then, we perform Pearson's chi-squared test to analyze the significance of the selected clinical and radiological features. Finally, we train machine classifiers based on different features and evaluate their ability to differentiate between DR-TB and DS-TB.
RESULTS: Pearson's chi-squared test shows that two clinical features and 23

radiological features are statistically significant regarding DR-TB vs. DS-TB. A ten-fold cross-validation using a support vector machine shows that automatic discrimination between DR-TB and DS-TB achieves an average accuracy of 72.34% and an average AUC value of 78.42%, when combing all 25 statistically significant features.
CONCLUSIONS: Our study suggests that the number of affected lung sextants can be used for predicting DR-TB, and that automatic discrimination between DR-TB and DS-TB is possible, with a combination of clinical features and radiological features providing the best performance.



DOI: 10.21037/qims-21-290
PMCID: PMC8666787
PMID: 34993110

15. **The pharmacotherapeutic management of pulmonary tuberculosis: an update of the state-of-the-art.**

Expert Opin Pharmacother. 2022 Jan;23(1):139-148. doi: 10.1080/14656566.2021.1967930. Epub 2021 Aug 21.

Fekadu G(1), Chow DY(1), You JHS(1).

INTRODUCTION: Pulmonary tuberculosis (TB) remains an important global health challenge of the 21st century, and the emerging resistance against anti-TB drugs is still a growing concern. And while there was a significant cumulative reduction in the incidence of TB between 2015 and 2019, 2.8% of all TB cases in 2019 were reported to be drug resistant.
AREA COVERED: This review provides the reader with an update on pharmacotherapy for patients with TB susceptible or resistant to drug therapy. The authors also include promising investigational drugs herein. Finally, the authors share with the reader their expert opinions on the current state of the art and their future perspectives.
EXPERT OPINION: The current pharmacotherapeutic management aims to enhance favorable treatment outcomes and reduce treatment-related adverse events. One approach is to use shorter and all-oral regimens for eligible patients. Traditional longer regimens for most patients are also optimized to lower incidence of treatment failure and serious adverse events.

DOI: 10.1080/14656566.2021.1967930
PMID: 34402698 [Indexed for MEDLINE]

16. **Hematologic Toxicity of Linezolid in Multidrug Resistant and Extensively Drug Resistant Tuberculosis (MDR/XDR-TB): the role of mitochondria.**

Tuberc Respir Dis (Seoul). 2022 Jan 20. doi: 10.4046/trd.2021.0122. Online ahead of print.

Oehadian A(1), Santoso P(1), Menzies D(2), Ruslami R(3).

Multidrug-resistant tuberculosis (MDR-TB) is resistant to both rifampicin and isoniazid. Extensively drug-resistant TB (XDR-TB) is a rare type of MDR-TB which is resistant to quinolone and one of the group A TB drugs, i.e., linezolid or bedaquiline. In 2018, the World Health Organization revised the groupings of TB medicines and reclassified linezolid as a group A drug for the treatment of MDR-TB. Linezolid is a synthetic antimicrobial agent in the oxazolidinone class. Although linezolid has good efficacy, it can cause substantial adverse events, especially hematologic toxicity. In both TB infection and linezolid mechanism of action, mitochondrial dysfunction plays an important role. In this concise review, linezolid characteristics as an antiTB drug are summarized, including its efficacy; pathogenesis of hematologic toxicity, highlighting mitochondrial dysfunction; and the monitoring and management of hematologic toxicity.

DOI: 10.4046/trd.2021.0122
PMID: 35045688

17. **Tuberculosis Pathways to Care and Transmission of Multidrug Resistance in India.**

Am J Respir Crit Care Med. 2022 Jan 15;205(2):233-241. doi: 10.1164/rccm.202012-4333OC.

Atre SR(1), Jagtap JD(1), Faqih MI(1), Dumbare YK(1), Sawant TU(1), Ambike SL(1), Bhawalkar JS(1), Bharaswadkar SK(2), Jogewar PK(3), Adkekar RS(3), Hodgar BP(4), Jadhav V(5), Mokashi ND(6), Golub JE(7), Dixit A(8)(9), Farhat MR(8)(10).

Rationale: India is experiencing a regional increase in cases of multidrug-resistant tuberculosis (MDR-TB). Objectives: Given the complexity of MDR-TB diagnosis and care, we sought to address key knowledge gaps in MDR risk factors, care delays, and drivers of delay to help guide disease control. Methods: From January 2018 to September 2019, we conducted interviews with adults registered with the National TB Elimination Program for MDR (n = 128) and non-MDR-TB (n = 269) treatment to quantitatively and qualitatively study care pathways. We collected treatment records and GeneXpert-TB/RIF diagnostic reports. Measurements and Main Results: MDR-TB was associated with young age and

crowded residence. GeneXpert rifampicin resistance diversity was measured at 72.5% Probe E. Median time from symptom onset to diagnosis of MDR was 90 days versus 60 days for non-MDR, Wilcoxon P < 0.01. Delay decreased by a median of 30 days among non-MDR patients with wider access to GeneXpert, Wilcoxon P = 0.02. Pathways to care were complex, with a median (interquartile range) of 4 (3-5) and 3 (2-4) encounters for MDR and non-MDR, respectively. Of patients with MDR-TB, 68% had their first encounter in the private sector, and this was associated with a larger number of subsequent healthcare encounters and catastrophic expenditure. Conclusions: The association of MDR with young age, crowding, and low genotypic diversity raises concerns of ongoing MDR transmission fueled by long delays in care. Delays are decreasing with GeneXpert use, suggesting the need for routine use in presumptive TB. Qualitatively, we identify the need to improve patient retention in the National TB Elimination Program and highlight patients' trust relationship with private providers.

DOI: 10.1164/rccm.202012-4333OC
PMID: 34706203

18. **Molecular Characteristic of Both Levofloxacin and Moxifloxacin Resistance in Mycobacterium tuberculosis from Individuals Diagnosed with Preextensive Drug-Resistant Tuberculosis.**

Microb Drug Resist. 2021 Dec 31. doi: 10.1089/mdr.2021.0212. Online ahead of print.

Zhang X(1), Chen X(2), Wang B(2), Fu L(2), Huo F(3), Gao T(1), Pang Y(4), Lu Y(2), Li Q(5).

Aim: Fluoroquinolones (FQs) are the cornerstone in treating drug-resistant tuberculosis (TB); the prevalence of TB among the population is diverse in different regions, understanding the relationship between resistance pattern and molecular characteristic of FQs in preextensive drug-resistant (pre-XDR) clinical isolates is limited in China. Methods: A total of 141 pre-XDR clinical isolates from different individuals stored at the National Clinical Centre were collected from the Beijing Chest Hospital, minimal inhibitory concentrations of levofloxacin (Lfx) and moxifloxacin (Mfx) as well as sequences of quinolone-resistant determining regions in gyrA and gyrB genes were examined. Results: One hundred twelve pre-XDR clinical isolates were resistant to both Lfx and Mfx, molecular analyses showed that 87.50%, 0.89%, and 6.25% of the pre-XDR clinical isolates harbored FQ resistance mutations in gyrA, gyrB, and in both. We found five amino acid mutation positions in gyrA and four in gyrB, The mutation position in gyrA included codons 94, 91, 90, 88, and 74, and in gyrB included codons 504, 500, 512, and 501. Codon 94 of gyrA was the most prevalent

mutation (83.04%), containing the Asp amino acid substitution with Gly (50.89%), Asn (15.17%), Ala (8.93%), Tyr (6.25%), and His (1.79%). Conclusions: The mutations of gyrA were most common and the frequency of Asp94Gly was the highest in pre-XDR clinical isolates in Beijing, China. The mutations at codon 94 significantly contributed to the resistance to both Lfx and Mfx in pre-XDR clinical isolates and may cause a high resistance level.

DOI: 10.1089/mdr.2021.0212
PMID: 34981969

19. **High-dose gatifloxacin-based shorter treatment regimens for MDR/RR-TB.**

Int J Infect Dis. 2022 Feb;115:142-148. doi: 10.1016/j.ijid.2021.11.037. Epub 2021 Nov 30.

Nie Q(1), Tao L(2), Li Y(3), Chen N(4), Chen H(4), Zhou Y(4), Wang Y(4), Chen H(5), Tang Q(4), Wang X(6), Huang C(7), Yang C(8).

SETTING: The shorter treatment regimen (STR) for multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB) has achieved successful outcomes in many countries. However, there are few studies on high-dose gatifloxacin-based STR with adverse drug reactions (ADRs) and management.
DESIGN: A prospective observational study was conducted with MDR/RR-TB patients who were treated with a standardized 9 or 12 - month regimen: including gatifloxacin (Gfx), clofazimine (Cfz), ethambutol (EMB), and pyrazinamide (PZA), and supplemented by amikacin (Am), isoniazid (INH), and prothionamide (Pto) during an intensive phase of 4 or 6 - month. Monitored ADRs monthly until treatment completion and then followed up every three months for one year.
RESULTS: Among the 42 eligible patients, 35 (83.3%) completed treatment successfully, 1 (2.4%) lost to follow-up (LTFU), and 6 (14.3%) failed due to ADRs, with no death. The most important ADR was drug-induced liver damage, which occurred in 24 out of 42 (57.1%) patients and resulted in 4 (9.5%) failed treatments and 4 (9.5%) adjusted treatments. QT interval prolongation occurred in 17 out of 42 (40.5%) patients, 9 (21.4%) of them with the corrected QT interval according to Fridericia (QTcF) > 500 ms resulting in 7 (16.7%) adjusted treatments.
CONCLUSIONS: This study confirmed the effectiveness of the high-dose gatifloxacin-based STR but severe ADRs, especially hepatotoxicity and QT interval prolongation should never be ignored.



DOI: 10.1016/j.ijid.2021.11.037

PMID: 34861398 [Indexed for MEDLINE]

20. **Utility of EBUS-TBNA in diagnosing mediastinal tuberculous lymphadenitis in East London.**

J Infect. 2022 Jan;84(1):17-23. doi: 10.1016/j.jinf.2021.10.015. Epub 2021 Oct 24.

Lucey O(1), Potter J(2), Ricketts W(2), Castle L(2), Melzer M(3).

OBJECTIVES: To characterise and describe the diagnostic utility of Endobronchial ultrasound-transbronchial needle aspiration (EBUS-TBNA) in intrathoracic tuberculosis in a cohort of patients with mediastinal lymphadenopathy of unknown aetiology.
METHODS: Consecutive patients with intrathoracic lymphadenopathy undergoing EBUS-TBNA between 2012 and 2016 were identified. Demographic data, biopsy cytopathology and mycobacteriology results, HIV and vitamin D status, susceptibility results and final diagnoses were recorded. Pre- and post-procedure probability scores were assigned to each case to reflect the probability of tuberculosis.
RESULTS: 315 cases were identified; 54 (17.1%) had tuberculosis and 261 (82.9%) had a non-tuberculosis diagnosis. amongst TB cases, the sensitivity of EBUS-TBNA was 59.3% (95% CI 45.06-72.14), specificity 100% (95% CI 98.19-100) and the negative predictive value (NPV) was 92.23% (95% CI 88.31-94.95). 19/54 (35%) TB cases were confirmed by EBUS mycobacterial culture and 13/54 (24.1%) by cytopathology. 33 (61.1%) of the TB cases, had a low to medium pre-test probability score assigned prior to EBUS-TBNA. Amongst EBUS culture-confirmed cases, we found a resistance rate of 10.5% to one or more first line TB drugs, with one case of multi-drug resistant TB.
CONCLUSIONS: We confirmed the utility of EBUS-TBNA in the diagnosis of intrathoracic tuberculosis in an undifferentiated cohort of patients with mediastinal lymphadenopathy of unknown aetiology and advocate sending samples for mycobacterial culture in all cases in high tuberculosis incidence areas.



DOI: 10.1016/j.jinf.2021.10.015
PMID: 34706281

21. **Screening approaches and therapeutic targets: The two driving wheels of tuberculosis drug discovery.**

Biochem Pharmacol. 2022 Jan 4;197:114906. doi: 10.1016/j.bcp.2021.114906. Online ahead of print.

Perveen S(1), Sharma R(2).

Tuberculosis (TB) is an infectious disease, infecting a quarter of world's population. Drug resistant TB further exacerbates the grim scenario of the drying TB drug discovery pipeline. The limited arsenal to fight TB presses the need for thorough efforts for identifying promising hits to combat the disease. The review highlights the efforts in the field of tuberculosis drug discovery, with an emphasis on massive drug screening campaigns for identifying novel hits against Mtb in both industry and academia. As an intracellular pathogen, mycobacteria reside in a complicated intracellular environment with multiple factors at play. Here, we outline various strategies employed in an effort to mimic the intracellular milieu for bringing the screening models closer to the actual settings. The review also focuses on the novel targets and pathways that could aid in target-based drug discovery in TB. The recent high throughput screening efforts resulting in the identification of potent hits against Mtb has been summarized in this article. There is a pressing need for effective screening strategies and approaches employing innovative tools and recent technologies; including nanotechnology, gene-editing tools such as CRISPR-cas system, host-directed bacterial killing and high content screening to augment the TB drug discovery pipeline with safer and shorter drug regimens.



DOI: 10.1016/j.bcp.2021.114906
PMID: 34990594

22. **Transcriptome signature of cell viability predicts drug response and drug interaction in Mycobacterium tuberculosis.**

Cell Rep Methods. 2021 Dec 20;1(8):None. doi: 10.1016/j.crmeth.2021.100123.

Srinivas V(1), Ruiz RA(1), Pan M(1), Immanuel SRC(1), Peterson EJR(1), Baliga NS(1)(2)(3)(4).

There is an urgent need for new drug regimens to rapidly cure tuberculosis. Here, we report the development of drug response assayer (DRonA) and "MLSynergy," algorithms to perform rapid drug response assays and predict response of Mycobacterium tuberculosis (Mtb) to drug combinations. Using a transcriptome signature for cell viability, DRonA detects Mtb killing by diverse

mechanisms in broth culture, macrophage infection, and patient sputum, providing an efficient and more sensitive alternative to time- and resource-intensive bacteriologic assays. Further, MLSynergy builds on DRonA to predict synergistic and antagonistic multidrug combinations using transcriptomes of Mtb treated with single drugs. Together, DRonA and MLSynergy represent a generalizable framework for rapid monitoring of drug effects in host-relevant contexts and accelerate the discovery of efficacious high-order drug combinations.



DOI: 10.1016/j.crmeth.2021.100123
PMCID: PMC8688151
PMID: 34977849

23. **Mycobacterium tuberculosis peritonitis in peritoneal dialysis patients: A scoping review.**

Nephrology (Carlton). 2022 Feb;27(2):133-144. doi: 10.1111/nep.13997. Epub 2021 Dec 6.

Thomson BKA(1)(2), Vaughan S(3), Momciu B(1).

BACKGROUND: The clinical syndrome of Mycobacterium tuberculosis (M. tuberculosis) peritoneal dialysis (PD) peritonitis is poorly understood. Whether local tuberculosis (TB) patterns modify the clinical syndrome, and what factors associate with poor outcomes is also unknown.
METHODS: A scoping review identified published cases of TB PD peritonitis. Cases from low- and high-TB burden areas were compared, and cases that did or did not suffer a poor clinical outcome were compared.
RESULTS: There were 216 cases identified. Demographics, presentation, diagnosis, treatment and outcomes were described. Significant delays in diagnosis were common (6.1 weeks) and were longer in patients from low-TB burden regions (7.3 vs. 3.7 weeks). In low-TB burden areas, slower diagnostic methods were more commonly used like PD fluid culture (64.3% vs. 32.7%), and treatment was less likely with quinolone antibiotics (6.9% vs. 34.1%). Higher national TB incidence and lower GDP per capita were found in cases that suffered PD catheter removal or death. Diagnostic delays were not longer in cases in which a patient suffered PD catheter removal or death. Cases that suffered death were older (51.9 vs. 45.1 years) and less likely female (37.8% vs. 55.7%). Removal of PD catheter was more common in cases in which a patient died (62.0% vs. 49.1%).
CONCLUSIONS: Outcomes in TB PD peritonitis are best predicted by national TB incidence, patient age and sex. Several unique features are identified to alert clinicians to use more rapid diagnostic methods that might enhance outcomes in

TB PD peritonitis.



DOI: 10.1111/nep.13997
PMID: 34743395

24. **Optimized loading dose strategies for bedaquiline when restarting interrupted drug-resistant tuberculosis treatment.**

Antimicrob Agents Chemother. 2022 Jan 10:AAC0174921. doi: 10.1128/AAC.01749-21. Online ahead of print.

Koele SE(1), van Beek SW(1), Maartens G(2)(3), Brust JCM(4), Svensson EM(1)(5).

Interruption of treatment is common in drug-resistant tuberculosis patients. Bedaquiline has a long terminal half-life therefore, restarting after an interruption without a loading dose could increase the risk of suboptimal treatment outcome and resistance development. We aimed to identify the most suitable loading dose strategies for bedaquiline restart after an interruption. A model-based simulation study was performed. Pharmacokinetic profiles of bedaquiline and its metabolite M2 (associated with QT-prolongation) were simulated for 5000 virtual patients for different durations and starting points of treatment interruption. Weekly bedaquiline area under the concentration-time curve (AUC) and M2 maximum concentration (Cmax) deviation before interruption and after reloading were assessed to evaluate the efficacy and safety respectively of the reloading strategies. Bedaquiline weekly AUC and M2 Cmax deviation were mainly driven by the duration of interruption and only marginally by the starting point of interruption. For interruptions with a duration shorter than two weeks, no new loading dose is needed. For interruptions with durations between two weeks and one month, one month and one year, and longer than one year, reloading periods of three days, one week, and two weeks, respectively, are recommended. This reloading strategy results in an average bedaquiline AUC deviation of 1.88% to 5.98% compared with -16.4% to -59.8% without reloading for interruptions of two weeks and one year respectively, without increasing M2 Cmax. This study presents easy-to-implement reloading strategies for restarting a patient on bedaquiline treatment after an interruption.

DOI: 10.1128/AAC.01749-21
PMID: 35007141

25. **Person-centred care and short oral treatment for rifampicin-resistant**

**tuberculosis improve retention in care in Kandahar, Afghanistan.**

Trop Med Int Health. 2022 Jan 3. doi: 10.1111/tmi.13716. Online ahead of print.

Mesic A(1)(2), Ishaq S(3), Khan WH(3), Mureed A(4), Mar HT(4), Khaing EE(4), Bermudez-Aza E(1), Rose L(3), Lynen L(2), Seddiq MK(5), Amirzada HK(5), Keus K(1), Decroo T(2)(6).

OBJECTIVES: To describe the effect of adaptations to a person-centred care with short oral regimens on retention in care for rifampicin-resistant TB (RR-TB) in Kandahar province, Afghanistan.
METHODS: The study included people with RR-TB registered in the programme between 01 October 2016 and 18 April 2021. From 19 November 2019, the programme implemented a trial investigating the safety and effectiveness of short oral RR-TB regimens. During the trial, person-centred care was adapted. We included the data from people living with RR-TB treated in the period before and after the care model was adapted and applied Kaplan-Meier statistics to compare rates of retention in care.
RESULTS: Of 236 patients registered in the RR-TB programme, 146 (61.9%) were registered before and 90 (38.1%) after the model of care was adapted. Before adaptations enhancing person-centred care, pre-treatment attrition was 23.3% (n = 34/146), whilst under the adapted care model it was 5.6% (n = 5/90). Attrition on treatment was 22.3% (n = 25/112) before adaptations, whilst during the study period none of the participants were lost-to-follow-up on treatment and 3.3% died (n = 3/90).
CONCLUSIONS: As person-centred care delivery and treatment regimens were adapted to better fit-specific contextual challenges and the needs of the target population, retention in care improved amongst people with RR-TB in Kandahar, Afghanistan.



DOI: 10.1111/tmi.13716
PMID: 34978748

26. **A modified decision tree approach to improve the prediction and mutation discovery for drug resistance in Mycobacterium tuberculosis.**

BMC Genomics. 2022 Jan 11;23(1):46. doi: 10.1186/s12864-022-08291-4.

Deelder W(1)(2), Napier G(1), Campino S(1), Palla L(1)(3), Phelan J(#)(1), Clark TG(#)(4)(5).

BACKGROUND: Drug resistant Mycobacterium tuberculosis is complicating the effective treatment and control of tuberculosis disease (TB). With the adoption of whole genome sequencing as a diagnostic tool, machine learning approaches are being employed to predict M. tuberculosis resistance and identify underlying genetic mutations. However, machine learning approaches can overfit and fail to identify causal mutations if they are applied out of the box and not adapted to the disease-specific context. We introduce a machine learning approach that is customized to the TB setting, which extracts a library of genomic variants re-occurring across individual studies to improve genotypic profiling.
RESULTS: We developed a customized decision tree approach, called Treesist-TB, that performs TB drug resistance prediction by extracting and evaluating genomic variants across multiple studies. The application of Treesist-TB to rifampicin (RIF), isoniazid (INH) and ethambutol (EMB) drugs, for which resistance mutations are known, demonstrated a level of predictive accuracy similar to the widely used TB-Profiler tool (Treesist-TB vs. TB-Profiler tool: RIF 97.5% vs. 97.6%; INH 96.8% vs. 96.5%; EMB 96.8% vs. 95.8%). Application of Treesist-TB to less understood second-line drugs of interest, ethionamide (ETH), cycloserine (CYS) and para-aminosalisylic acid (PAS), led to the identification of new variants (52, 6 and 11, respectively), with a high number absent from the TB-Profiler library (45, 4, and 6, respectively). Thereby, Treesist-TB had improved predictive sensitivity (Treesist-TB vs. TB-Profiler tool: PAS 64.3% vs. 38.8%; CYS 45.3% vs. 30.7%; ETH 72.1% vs. 71.1%).
CONCLUSION: Our work reinforces the utility of machine learning for drug resistance prediction, while highlighting the need to customize approaches to the disease-specific context. Through applying a modified decision learning approach (Treesist-TB) across a range of anti-TB drugs, we identified plausible resistance-encoding genomic variants with high predictive ability, whilst potentially overcoming the overfitting challenges that can affect standard machine learning applications.



DOI: 10.1186/s12864-022-08291-4
PMCID: PMC8753810
PMID: 35016609 [Indexed for MEDLINE]

27. **Safety of treatment regimens containing bedaquiline and delamanid in the endTB cohort.**

Clin Infect Dis. 2022 Jan 13:ciac019. doi: 10.1093/cid/ciac019. Online ahead of print.

Hewison C(1), Khan U(2), Bastard M(3), Lachenal N(4), Coutisson S(4), Osso E(5), Ahmed S(6), Khan P(2), Franke MF(5), Rich ML(5)(7), Varaine F(1), Melikyan N(3), Seung KJ(5)(7), Adenov M(8), Adnan S(9), Danielyan N(10), Islam S(11), Janmohamed A(6), Karakozian H(12), Kimenye MK(13), Kirakosyan O(14), Kholikulov B(15), Krisnanda A(16), Kumsa A(17), Leblanc G(18), Lecca L(19), Nkuebe M(20), Mamsa S(9), Padayachee S(21), Thit P(22), Mitnick CD(5)(7), Huerga H(3); endTB study observational study team.

RATIONALE: Safety of treatment for multidrug-resistant tuberculosis (MDR/RR-TB) can be an obstacle to treatment completion.
OBJECTIVES: Evaluate safety of longer MDR/RR-TB regimens containing bedaquiline and/or delamanid.
METHODS: Multicentre (16 countries), prospective, observational study, reporting incidence and frequency of clinically relevant adverse events of special interest (AESI) amongst patients who received MDR/RR-TB treatment containing bedaquiline and/or delamanid. The AESIs were defined a priori as important events caused by bedaquiline, delamanid, linezolid, injectables, and other commonly used drugs. Occurrence of these events was also reported by exposure to the likely causative agent.
RESULTS: Among 2296 patients, the most common clinically relevant AESIs were: peripheral neuropathy in 26.4%, electrolyte depletion in 26.0%, and hearing loss in 13.2% of patients. Per 1000 person-months of treatment, the incidence of these events was 21.5 (95% confidence interval [CI]: 19.8-23.2), 20.7 (95% CI: 19.1-22.4), and 9.7 (95% CI: 8.6-10.8), respectively. QT interval was prolonged in 2.7% or 1.8 (95% CI: 1.4-2.3)/1000 person-months of treatment. Patients who received injectables (N=925) and linezolid (N=1826) were most likely to experience events during exposure: Hearing loss, acute renal failure, or electrolyte depletion occurred in 36.8% or 72.8 (95%CI: 66.0-80.0) times/1000 person-months of injectable drug exposure. Peripheral neuropathy, optic neuritis and/or myelosuppression occurred in 27.8% or 22.8 (95% CI: 20.9-24.8) times/1000 patient-months of linezolid exposure.
CONCLUSIONS: Adverse events often related to linezolid and injectable drugs were more common than those frequently attributed to bedaquiline and delamanid. MDR-TB treatment monitoring schedules and individual drug durations should reflect expected safety profiles of drug combinations.



DOI: 10.1093/cid/ciac019
PMID: 35028659

28. **Mapping twenty years of antimicrobial resistance research trends.**

Artif Intell Med. 2022 Jan;123:102216. doi: 10.1016/j.artmed.2021.102216. Epub 2021 Nov 20.

Luz CF(1), van Niekerk JM(2), Keizer J(3), Beerlage-de Jong N(4), Braakman-Jansen LMA(3), Stein A(5), Sinha B(6), van Gemert-Pijnen JEWC(4), Glasner C(6).

OBJECTIVE: Antimicrobial resistance (AMR) is a global threat to health and healthcare. In response to the growing AMR burden, research funding also increased. However, a comprehensive overview of the research output, including conceptual, temporal, and geographical trends, is missing. Therefore, this study uses topic modelling, a machine learning approach, to reveal the scientific evolution of AMR research and its trends, and provides an interactive user interface for further analyses.
METHODS: Structural topic modelling (STM) was applied on a text corpus resulting from a PubMed query comprising AMR articles (1999-2018). A topic network was established and topic trends were analysed by frequency, proportion, and importance over time and space.
RESULTS: In total, 88 topics were identified in 158,616 articles from 166 countries. AMR publications increased by 450% between 1999 and 2018, emphasizing the vibrancy of the field. Prominent topics in 2018 were Strategies for emerging resistances and diseases, Nanoparticles, and Stewardship. Emerging topics included Water and environment, and Sequencing. Geographical trends showed prominence of Multidrug-resistant tuberculosis (MDR-TB) in the WHO African Region, corresponding with the MDR-TB burden. China and India were growing contributors in recent years, following the United States of America as overall lead contributor.
CONCLUSION: This study provides a comprehensive overview of the AMR research output thereby revealing the AMR research response to the increased AMR burden. Both the results and the publicly available interactive database serve as a base to inform and optimise future research.



DOI: 10.1016/j.artmed.2021.102216
PMID: 34998519

29. **Telacebec: an investigational antibiotic for the treatment of tuberculosis (TB).**

Expert Opin Investig Drugs. 2022 Jan 15. doi: 10.1080/13543784.2022.2030309. Online ahead of print.

Lee BS(1), Pethe K(1)(2).

INTRODUCTION: Tuberculosis is a leading cause of death by an infectious agent and has affected more than 50 million people and killed 6.7 million patients in the past 5 years alone. Rising incidence of resistance to treatment threatens the global effort to eradicate the disease. With limited options available, additional novel antibiotics are needed to form efficacious combinations for the treatment of multi-drug resistant tuberculosis (MDR-TB). Telacebec is a first-in-class antibiotic that inhibits growth of mycobacterium tuberculosis by targeting its energy metabolism. The compound has undergone three clinical studies, the latest being a phase 2a efficacy trial.
AREAS COVERED: This paper provides an overview of the recent progress in the development and testing of telacebec. We discuss published clinical data and examine the design and set up of its clinical trials. We also offer insights on the therapeutic potential of telacebec and aspects of which should be evaluated in the future.
EXPERT OPINION: The first phase 2a trial showed a correlation between dosage and bacterial load in patient sputum which should be confirmed using a direct measurement method such as colony-forming unit counting. Its clinical efficacy, favourable pharmacokinetic properties, low arrhythmogenic risk, and activity against MDR-TB strains make telacebec a suitable candidate for further development. Future clinical testing in combination with approved second-line drugs will reveal its full potential against MDR-TB. Considering recent preclinical studies, we also recommend initiating clinical trials for Buruli ulcer and leprosy.

DOI: 10.1080/13543784.2022.2030309
PMID: 35034512

30. **An Overview of Zinc Oxide Nanoparticles Produced by Plant Extracts for Anti-tuberculosis Treatments.**

Curr Med Chem. 2022;29(1):86-98. doi: 10.2174/0929867328666210614122109.

Behzad F(1), Sefidgar E(2), Samadi A(3), Lin W(4), Pouladi I(5), Pi J(4).

Tuberculosis (TB), induced by Mycobacterium tuberculosis (MTB), is a fatal infectious disease that kills millions of lives worldwide. The emergence of drug-resistant and multidrug-resistant cases is regarded as one of the most challenging threats to TB control due to the low cure rate. Therefore, TB and drug-resistant TB epidemic urge us to explore more effective therapies. The increasing knowledge of nanotechnology has extended the use of some nanomedicines for disease treatment in clinics, which also provide novel

possibilities for nano-based medicines for TB treatment. Zinc oxide nanoparticles (ZnO NPs) have gained increasing attention for anti-bacterial uses based on their strong ability to induce reactive oxidative species (ROS) and release bactericidal Zinc ions (Zn2+), which are expected to act as novel strategies for TB and drug-resistant TB treatment. Some plant extracts, always from active herbal medicines, have been widely reported to show attractive anti-bacterial activity for infectious treatment, including TB. Here, we summarize the synthesis of ZnO NPs using plant extracts (green synthesized ZnO NPs), and further discuss their potentials for anti-TB treatments. This is the first review article discussing the anti-TB activity of ZnO NPs produced using plant extracts, which might contribute to the further applications of green synthesized ZnO NPs for anti-TB and drugresistant TB treatment.



DOI: 10.2174/0929867328666210614122109
PMID: 34126883 [Indexed for MEDLINE]

31. **Antimycobacterial activity of acetone extract and isolated metabolites from folklore medicinal lichen Usnea laevis Nyl. against drug-sensitive and multidrug-resistant tuberculosis strains.**

J Ethnopharmacol. 2022 Jan 10;282:114641. doi: 10.1016/j.jep.2021.114641. Epub 2021 Sep 15.

Tatipamula VB(1), Annam SSP(2).

ETHNOPHARMACOLOGICAL RELEVANCE: Tuberculosis (Tb) is one of the most infectious diseases caused by Mycobacterium tuberculosis (M.t) with almost 2 million deaths yearly. Although many Tb control programs have been organised, there is an elevated number of Tb cases due to the appearance of extremely drug-resistant and multidrug-resistant (MDR) Tb strains. In the cultures of Venezuelan Andes, fruticose lichen Usnea laevis Nyl. (Usneaceae) with folklore name 'Barba de Piedra, Tusinya' is used as a natural remedy for Tb.
AIM OF THE STUDY: This study was performed to provide a scientific rationale for the folklore usage of U. laevis in treating Tb by validating its antimycobacterial activity against two drug-sensitive and four MDR-Tb strains.
MATERIALS AND METHODS: The mycobacterial inhibitory activities of acetone extract (Ul), fractions (F1-10), and isolated metabolites (1-4) of U. laevis were evaluated against M.t H37Ra using 2,3-bis-(2-methoxy-4-nitro-5-sulfophenyl)-2H-tetrazolium-5-carboxanilide reduction menadione assay (XRMA). Furthermore, Ul and 1-4 were subjected to

antimycobacterial activity against M.t H37Ra, Mycobacterium smegmatis, and four MDR-Tb (MDR-A8, MDR-V791, MDR-R and MDR-40) strains using resazurin microtitre plate assay (REMA) and cytotoxicity against THP-1 macrophages using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay and their selectivity index values were also calculated.
RESULTS: Initially, Ul has shown prominent inhibitory activity (IC50 value: 5.44 ± 0.36 μg/ml) and four of its fractions (F1, F2, F5 and F7) also exhibited the best inhibitory activity (IC50 values ranged from 7.46 ± 0.19 to 71.38 ± 2.57 μg/ml) against M.t H37Ra using XRMA. Purification of these bioactive fractions identified four metabolites, namely usnic acid (1), atranorin (2), salazinic acid (3), and lobaric acid (4). From the MIC values of REMA, it was identified that Ul, 1 and 4 were more effective in inhibiting the growth of all four MDR-Tb strains, compared to first-line drug rifampicin. Interestingly, Ul has shown better antimycobacterial activity than 1-4 and rifampicin against MDR-Tb strains may be due to the synergistic effect of its metabolites. Also, the IC50 values of Ul and 1-4 on THP-1 macrophages were found to be far higher than MIC values against tested Tb strains, indicating that THP-1 macrophages were not harmfully affected at concentrations that were effective against Tb strains. Further, the calculated selectivity index values revealed the more active and non-toxicity of Ul, 1 and 4 against MDR-Tb strains than rifampicin.
CONCLUSIONS: The current study lends the first evidence for the presence of antimycobacterial metabolites in U. laevis. The results exposed the Andean folklore use of U. laevis for treating Tb, and the key biomarker metabolites were found to be 1 and 4. Hence, it can be concluded that U. laevis can be used as a potential source for the novel drug development for MDR-Tb.



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PMID: 34536516

32. **Safety, Tolerability, and Pharmacokinetics of Telacebec (Q203), a New Antituberculosis Agent, in Healthy Subjects.**

Antimicrob Agents Chemother. 2022 Jan 18;66(1):e0143621. doi: 10.1128/AAC.01436-21. Epub 2021 Oct 25.

Kim J(1)(2), Choi J(2), Kang H(2), Ahn J(2), Hutchings J(2), van Niekerk C(2), Park D(2), Kim J(2), Jeon Y(2), Nam K(2), Shin S(#)(3), Shin BS(#)(1).

Telacebec (Q203) is a potent drug candidate under clinical development for the treatment of drug-naïve and drug-resistant tuberculosis. The first-in-human

randomized, placebo-controlled, double-blind, dose-escalation Phase 1A trial (Q203-TB-PI-US001) was conducted to evaluate the safety, tolerability, and pharmacokinetics of telacebec. A total of 56 normal, healthy, male and female subjects (42 active and 14 placebo) were enrolled in the study. The doses of telacebec were 10 mg (Cohort 1), 30 mg (Cohort 2), 50 mg (Cohort 3), 100 mg (Cohort 4), 200 mg (Cohort 5), 400 mg (Cohort 6), and 800 mg (Cohort 7) in a fasted state. Subjects participating in Cohort 4 were also enrolled in Cohort 8 to investigate the food effect on the pharmacokinetics of telacebec after a high-fat meal. In all subjects dosed with telacebec (10 to 800 mg), telacebec was well tolerated and did not lead to any significant or serious adverse events. Following a single oral administration of telacebec (10 to 800 mg), telacebec plasma concentration reached the maximal plasma concentration (Cmax) in average 2.0 to 3.5 h and showed multi-exponential decline thereafter. The area under the plasma concentration versus time curve (AUC) was approximately dose-proportional. A significant increase in plasma concentrations was observed in the fed condition compared with the fasted condition with the geometric mean ratio of 3.93 for Cmax. Moderate delay in Tmax (4.5 h) was also observed in the fed condition. These results, combined with the demonstrated activity against drug-sensitive and multidrug-resistant Mycobacterium tuberculosis, support further investigation of telacebec for the treatment of tuberculosis.

DOI: 10.1128/AAC.01436-21
PMID: 34694872

33. **A Rapid Drug Resistance Genotyping Workflow for Mycobacterium tuberculosis, Using Targeted Isothermal Amplification and Nanopore Sequencing.**

Microbiol Spectr. 2021 Dec 22;9(3):e0061021. doi: 10.1128/Spectrum.00610-21. Epub 2021 Nov 24.

Gliddon HD(#)(1)(2), Frampton D(#)(3), Munsamy V(4), Heaney J(5), Pataillot-Meakin T(5), Nastouli E(5), Pym AS(4), Steyn AJC(4)(6), Pillay D(3)(4), McKendry RA(1)(7).

Phenotypic drug susceptibility testing (DST) for tuberculosis (TB) requires weeks to yield results. Although molecular tests rapidly detect drug resistance-associated mutations (DRMs), they are not scalable to cover the full genome and the many DRMs that can predict resistance. Whole-genome sequencing (WGS) methods are scalable, but if conducted directly on sputum, typically require a target enrichment step, such as nucleic acid amplification. We developed a targeted isothermal amplification-nanopore sequencing workflow for rapid prediction of drug resistance of TB isolates. We used recombinase polymerase amplification (RPA) to perform targeted isothermal amplification

(37°C for 90 min) of three regions within the Mycobacterium tuberculosis genome, followed by nanopore sequencing on the MinION. We tested 29 mycobacterial genomic DNA extracts from patients with drug-resistant (DR) TB and compared our results to those of WGS by Illumina and phenotypic DST to evaluate the accuracy of prediction of resistance to rifampin and isoniazid. Amplification by RPA showed fidelity equivalent to that of high-fidelity PCR (100% concordance). Nanopore sequencing generated DRM predictions identical to those of WGS, with considerably faster sequencing run times of minutes rather than days. The sensitivity and specificity of rifampin resistance prediction for our workflow were 96.3% (95% confidence interval [CI], 81.0 to 99.9%) and 100.0% (95% CI, 15.8 to 100.0%), respectively. For isoniazid resistance prediction, the sensitivity and specificity were 100.0% (95% CI, 86.3 to 100.0%) and 100.0% (95% CI, 39.8 to 100.0%), respectively. The workflow consumable costs per sample are less than £100. Our rapid and low-cost drug resistance genotyping workflow provides accurate prediction of rifampin and isoniazid resistance, making it appropriate for use in resource-limited settings. IMPORTANCE Current methods for diagnosing drug-resistant tuberculosis are time consuming, resulting in delays in patients receiving treatment and in transmission onwards. They also require a high level of laboratory infrastructure, which is often only available at centralized facilities, resulting in further delays to diagnosis and additional barriers to deployment in resource-limited settings. This article describes a new workflow that can diagnose drug-resistant TB in a shorter time, with less equipment, and for a lower price than current methods. The amount of TB DNA is first increased without the need for bulky and costly thermocycling equipment. The DNA is then read using a portable sequencer called a MinION, which indicates whether there are tell-tale changes in the DNA that indicate whether the TB strain is drug resistant. Our workflow could play an important role in the future in the fight against the public health challenge that is TB drug resistance.

DOI: 10.1128/Spectrum.00610-21
PMCID: PMC8612157
PMID: 34817282

34. **Public health and hospital-based nursing intersection: Case study of drug-resistant tuberculosis patients.**

Public Health Nurs. 2022 Jan;39(1):170-179. doi: 10.1111/phn.13042. Epub 2022 Jan 6.

Pietersen E(1), Anderson K(1)(2), van der Heijden YF(3)(4)(5).

OBJECTIVE: Public health nurses (PHN) are key partners in continuity of care for

drug-resistant tuberculosis (DR-TB) patients. We examined complexities in DR-TB care transition between community- and hospital-based care.
DESIGN: We conducted a case study using medical record data. Four patients were purposively selected to illustrate intersectional complexities in DR-TB care transition involving PHN.
RESULTS: Case A (HIV negative male) received PHN care at a community-based facility 124 km from Cape Town. Cases B, C, and D (males living with HIV) received PHN community-based care, averaging 25 km from the hospital. Treatment failed in cases A, B, and C; they subsequently died. Case D was cured. All cases were granted leave of absence at least once while hospitalized. None returned when expected mainly due to lack of transport funds. PHN played critical roles regarding patients' return by conducting home visits, interacting with relatives, and assisting emergency officers to transport patients back to the hospital. PHN supported relatives to endure protracted patient hospitalizations.
CONCLUSION: The role of PHN in continuity of DR-TB care in low-middle income countries is unambiguous. PHN are key partners in the DR-TB care cascade, namely facilitating retention in care between hospital and community-based care. Effective DR-TB control relies on effective partnerships among healthcare personnel, patients, and their families.



DOI: 10.1111/phn.13042
PMCID: PMC8766955
PMID: 34990027

35. **Detection of minor variants in Mycobacterium tuberculosis whole genome sequencing data.**

Brief Bioinform. 2021 Dec 27:bbab541. doi: 10.1093/bib/bbab541. Online ahead of print.

Goossens SN(1), Heupink TH(1), De Vos E(1), Dippenaar A(1), De Vos M(2), Warren R(3), Van Rie A(1).

The study of genetic minority variants is fundamental to the understanding of complex processes such as evolution, fitness, transmission, virulence, heteroresistance and drug tolerance in Mycobacterium tuberculosis (Mtb). We evaluated the performance of the variant calling tool LoFreq to detect de novo as well as drug resistance conferring minor variants in both in silico and clinical Mtb next generation sequencing (NGS) data. The in silico simulations demonstrated that LoFreq is a conservative variant caller with very high precision (≥96.7%) over the entire range of depth of coverage tested (30x

to1000x), independent of the type and frequency of the minor variant. Sensitivity increased with increasing depth of coverage and increasing frequency of the variant, and was higher for calling insertion and deletion (indel) variants than for single nucleotide polymorphisms (SNP). The variant frequency limit of detection was 0.5% and 3% for indel and SNP minor variants, respectively. For serial isolates from a patient with DR-TB; LoFreq successfully identified all minor Mtb variants in the Rv0678 gene (allele frequency as low as 3.22% according to targeted deep sequencing) in whole genome sequencing data (median coverage of 62X). In conclusion, LoFreq can successfully detect minor variant populations in Mtb NGS data, thus limiting the need for filtering of possible false positive variants due to sequencing error. The observed performance statistics can be used to determine the limit of detection in existing whole genome sequencing Mtb data and guide the required depth of future studies that aim to investigate the presence of minor variants.



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PMID: 34962257

36. **Diagnostic accuracy of Truenat Tuberculosis and Rifampicin-Resistance assays in Addis Ababa, Ethiopia.**

PLoS One. 2021 Dec 28;16(12):e0261084. doi: 10.1371/journal.pone.0261084. eCollection 2021.

Meaza A(1)(2), Tesfaye E(1), Mohamed Z(1), Zerihun B(1), Seid G(1), Eshetu K(1), Amare M(1), Sinshaw W(1), Dagne B(1), Mollalign H(1), Diriba G(1), Getu M(1), Yenew B(1), Tadesse M(1), Fikadu D(1), Abebaw Y(1), Moga S(1), Kebede A(1), Tola HH(1), Alemu A(1), Getahun M(1), Gumi B(2).

BACKGROUND: Rapid and sensitive Tuberculosis (TB) diagnosis closer to patients is a key global TB control priority. Truenat assays (MTB, MTB Plus, and MTB-RIF Dx) are new TB molecular diagnostic tools for the detection of TB and Rifampicin (RIF)-resistance from sputum samples. The diagnostic accuracy of the assays is needed prior to implementation in clinical use in Ethiopia. This study aimed to determine the sensitivity and specificity of Truenat assays; and aimed to compare the assays to the Xpert MTB/RIF assay.
METHODS: A prospective evaluation study was conducted among 200 presumptive TB patients in microscopy centers in Addis Ababa, Ethiopia from May 2019 to December 2020. Culture (Solid and Liquid methods) and phenotypic (liquid method) drug susceptibility testing (DST) were used as a reference standard.
RESULTS: Of 200 adult participants, culture confirmed TB cases were 25 (12.5%),

and only one isolate was resistant to RIF by phenotypic DST. The sensitivity of Truenat MTB was 88.0% [95% CI 70.1, 95.8], while 91.7 [95% CI 74.2, 97.7] for Truenat MTB Plus at the microscopy centers. The specificity of Truenat MTB was 97.2% [95% CI 93.1, 98.9], while for Truenat MTB Plus was 97.2% [95% CI 93.0, 99.0]. The sensitivity of Truenat MTB was 90.5% while for MTB Plus, 100% compared to the Xpert MTB/RIF assay.
CONCLUSION: Truenat assays were found to have high diagnostic accuracy. The assays have the potential to be used as a point of care (POC) TB diagnostic tests.

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PMCID: PMC8714111
PMID: 34962949 [Indexed for MEDLINE]

37. **Strategies employed to evade the host immune response and the mechanism of drug resistance in Mycobacterium tuberculosis: In search of finding new targets.**

Curr Pharm Biotechnol. 2021 Dec 22. doi: 10.2174/1389201023666211222164938. Online ahead of print.

Sheikh BA(1), Bhat BA(1), Ahmad Z(2), Mir MA(1).

The partial effectiveness of the host immune response to M. tuberculosis drives bacteria into a latent state, but it is difficult to eliminate the bacteria completely. Usually, this latent condition of M. tuberculosis is reversible, and reactivation of tuberculosis is the leading cause of the majority of transmission. A number of studies performed on animal models and in humans have not yet provided a detailed understanding of the mechanisms or correlates of immunity of M. tuberculosis infection or why there is a significant immunity failure to remove the pathogen. Moreover, the mechanism of resistance involved in drug-resistant M. tuberculosis leading to the emergence of strains of bacteria that show significant resistance to the majority of anti-tuberculosis drugs. We have also provided the recent findings and trends regarding the development of new drug molecules to treat drug and multidrug-resistant tuberculosis and the advancements in immunotherapy in the treatment of drug-resistant tuberculosis. This article provides an in-depth and critical analysis of various strategies employed by the drug-resistant M. tuberculosis to escape the host immune response, as a result of which this bacterium persists in the host for a longer period of time and leads to the development of tuberculosis infection. Furthermore, we also discussed the new targets for the effective treatment of drug resistant tuberculosis.

epub@benthamscience.net.

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PMID: 34951359

38. **An updated patent review on drugs for the treatment of tuberculosis (2018-present).**

Expert Opin Ther Pat. 2021 Dec 30:1-18. doi: 10.1080/13543776.2022.2012151. Online ahead of print.

Ahmed S(1), Nandi S(1), Saxena AK(1).

INTRODUCTION: Tuberculosis (TB) caused by Mycobacterium tuberculosis (M.tb) has been a global challenge as 1.4 million deaths were reported in 2019, which included deaths attributed to HIV-TB co-infection. It is curable by the prescribed Directly Observed Treatment Short (DOTS) course, but the situation becomes critical and alarming due to multi-drug resistant (MDR) and extensively drug-resistant (XDR) tuberculosis. Hence there has been an urgent need to develop novel M.tb chemotherapeutics to overcome this situation.
AREAS COVERED: This review provides an overview and update on recent developments on the novel therapeutics for the treatment of TB from the important published and granted patents (2018-present).
EXPERT OPINION: The discovery of potent chemotherapeutics with reduced toxicity to combat M.tb particularly MDR and XDR-TB is a major challenge in antitubercular drug development. The missing of any doses during the DOTS treatment and poor immunity particularly in HIV patients has been a major cause for the development of drug resistance. Hence the major focus has to be on novel targets with their inhibitors and novel molecules both of natural and synthetic origins along with repurposed drugs for the complete eradication of tuberculosis.

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PMID: 34846976

39. **Comparative Performance of Genomic Methods for the Detection of Pyrazinamide Resistance and Heteroresistance in Mycobacterium tuberculosis.**

J Clin Microbiol. 2022 Jan 19;60(1):e0190721. doi: 10.1128/JCM.01907-21. Epub 2021 Nov 10.

Whitfield MG(1)(2)(3), Engelthaler DM(4), Allender C(4), Folkerts M(4), Heupink

TH(2), Limberis J(5), Warren RM(3), Van Rie A(#)(2), Metcalfe JZ(#)(5).

Pyrazinamide is an important component of both drug-susceptible and drug-resistant tuberculosis treatment regimens. Although approximately 50% of rifampin-resistant isolates are also resistant to pyrazinamide, pyrazinamide susceptibility testing is not routinely performed due to the challenging nature of the assay. We investigated the diagnostic accuracy of genotypic and phenotypic methods and explored the occurrence of pyrazinamide heteroresistance. We assessed pyrazinamide susceptibility among 358 individuals enrolled in the South African EXIT-RIF cohort using Sanger and targeted deep sequencing (TDS) of the pncA gene, whole-genome sequencing (WGS), and phenotypic drug susceptibility testing. We calculated the diagnostic accuracy of the different methods and investigated the prevalence and clinical impact of pncA heteroresistance. True pyrazinamide susceptibility status was assigned to each isolate using the Köser classification and expert rules. We observed 100% agreement across genotypic methods for detection of pncA fixed mutations; only TDS confidently identified three isolates (0.8%) with minor variants. For the 355 (99.2%) isolates that could be assigned true pyrazinamide status with confidence, phenotypic DST had a sensitivity of 96.5% (95% confidence interval [CI], 93.8 to 99.3%) and specificity of 100% (95% CI, 100 to 100%), both Sanger sequencing and WGS had a sensitivity of 97.1% (95% CI, 94.6 to 99.6%) and specificity of 97.8% (95% CI, 95.7 to 99.9%), and TDS had sensitivity of 98.8% (95% CI, 97.2 to 100%) and specificity of 97.8% (95% CI, 95.7 to 99.9%). We demonstrate high sensitivity and specificity for pyrazinamide susceptibility testing among all assessed genotypic methods. The prevalence of pyrazinamide heteroresistance in Mycobacterium tuberculosis isolates was lower than that identified for other first-line drugs.

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PMID: 34757831

40. **Improving healthcare for patients with HIV, tuberculosis and hepatitis C in eastern Europe: a review of current challenges and important next steps.**

HIV Med. 2022 Jan;23(1):48-59. doi: 10.1111/hiv.13163. Epub 2021 Sep 1.

Kraef C(1)(2)(3), Bentzon A(1), Skrahina A(4), Mocroft A(1)(5), Peters L(1), Lundgren JD(1)(2), Chkhartishvili N(6)(7), Podlekareva D(1)(2), Kirk O(1)(2).

OBJECTIVES: In some eastern European countries, serious challenges exist to meet the HIV-, tuberculosis (TB)- and hepatitis-related target of the United Nations Sustainable Development Goals. Some of the highest incidence rates for HIV and the highest proportion of multi-drug-resistant (MDR) tuberculosis worldwide are

found in the region. The purpose of this article is to review the challenges and important next steps to improve healthcare for people living with TB, HIV and hepatitis C (HCV) in eastern Europe.
METHODS: References for this narrative review were identified through systematic searches of PubMed using pre-idientified key word for articles published in English from January 2000 to August 2020. After screening of titles and abstracts 37 articles were identified as relevant for this review. Thirty-eight further articles and sources were identified through searches in the authors' personal files and in Google Scholar.
RESULTS: Up to 50% of HIV/MDR-TB-coinfected individuals in the region die within 2 years of treatment initiation. Antiretroviral therapy (ART) coverage for people living with HIV (PLHIV) and the proportion virological suppressed are far below the UNAIDS 90% targets. In theory, access to various diagnostic tests and treatment of drug-resistant TB exists, but real-life data point towards inadequate testing and treatment. New treatments could provide elimination of viral HCV in high-risk populations but few countries have national programmes.
CONCLUSION: Some eastern European countries face serious challenges to achieve the sustainable development goal-related target of 3.3 by 2030, among others, to end the epidemics of AIDS and tuberculosis. Better integration of healthcare systems, standardization of health care, unrestricted substitution therapy for all people who inject drugs, widespread access to drug susceptibility testing, affordable medicines and a sufficiently sized, well-trained health workforce could address some of those challenges.



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PMID: 34468073

41. **Predictors of mortality among TB-HIV co-infected children attending anti-retroviral therapy clinics of selected public hospitals in southern, Ethiopia: retrospective cohort study.**

Arch Public Health. 2022 Jan 4;80(1):11. doi: 10.1186/s13690-021-00713-1.

Gemechu J(1), Gebremichael B(2), Tesfaye T(2), Seyum A(1), Erkalo D(3).

BACKGROUND: Co-infection of tuberculosis and HIV has a significant impact on public health. TB is the most common opportunistic infection and the leading cause of death in HIV-positive children worldwide. But there is paucity of studies concerning the predictors of mortality among TB-HIV co-infected children. This study aimed to determine the predictors of mortality among TB-HIV

co-infected children attending ART clinics of public hospitals in Southern Nation, Nationalities and Peoples Region (SNNPR), Ethiopia.
METHODS: A hospital-based retrospective cohort study design was used among 284 TB-HIV co-infected children attending ART clinics at selected public hospitals in SNNPR, Ethiopia, from January 2009 to December 2019. Then, medical records of children who were TB/HIV co-infected and on ART were reviewed using a structured data extraction tool. Data were entered using Epidata 4.6 and analyzed using SPSS version 23. The Kaplan Meier survival curve along with log rank tests was used to estimate and compare survival time. Bivariable and multivariable analyses were conducted to identify predictors of mortality among TB/HIV co-infected children. Adjusted Hazard Ratio with p value < 0.05 and 95% confidence interval was considered statistically significant.
RESULT: A total of 284 TB/HIV co-infected children were included in the study. Among these, 35 (12.3%) of them died during the study period. The overall mortality rate was 2.78 (95%CI = 1.98-3.99) per 100 child years of observation. The predictors of mortality were anemia (AHR = 3.6; 95%CI: 1.39-9.31), fair or poor ART drug adherence (AHR = 2.9; 95%CI = 1.15-7.43), extrapulmonary TB (AHR = 3.9; 95%CI: 1.34-11.45) and TB drug resistance (AHR = 5.7; 95%CI: 2.07-15.96).
CONCLUSION: Mortality rate of TB/HIV co-infected children in selected public hospitals in SNNPR, Ethiopia was documented as 2.78 per child years of observation as a result of this study. Moreover, Anemia, drug resistant tuberculosis, extrapulmonary TB and poor adherence to ART drugs were identified as the predictors of mortality among these children.



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PMCID: PMC8728901
PMID: 34983618

42. **New silver(I) phosphino complexes: Evaluation of their potential as prospective agents against Mycobacterium tuberculosis.**

J Inorg Biochem. 2022 Feb;227:111683. doi: 10.1016/j.jinorgbio.2021.111683. Epub 2021 Dec 3.

Maldonado YD(1), Scalese G(2), Manieri KF(3), Pavan FR(3), Aguirre Méndez LD(4), Gambino D(5).

Despite being a preventable and curable disease, Tuberculosis (TB) is the world's top infectious killer. Development of new drugs is urgently needed. In this work, the synthesis and characterization of new silver(I) complexes, that

include N'-[(E)-(pyridine-2-ylmethylene)pyrazine-2-carbohydrazide, HPCPH, as main ligand and substituted aryl-phosphines as auxiliary ligands, is reported. HPCPH was synthesized from pyrazinoic acid, the active metabolite of the first-line antimycobacterial drug pyrazinamide. Complexes [Ag(HPCPH)(PPh3)2]OTf (1), [Ag(HPCPH)((P(p-tolyl)3)2]OTf (2) and [Ag(HPCPH)(P(p-anisyl)3)2]OTf (3) were characterized in solid state and in solution by elemental analysis and FTIR and NMR spectroscopies (OTftriflate). Crystal structures of (1,2) were determined by XRD. The Ag atom is coordinated to azomethine and pyridine nitrogen atoms of HPCPH ligand and to the phosphorous atom of each aryl-phosphine co-ligand. Although HPCPH did not show activity, the Ag(I) compounds demonstrated activity against Mycobacterium tuberculosis (MTB), H37Rv strain, and multi-drug resistant clinical isolates (MDR-TB). Globally, results showed that the compounds are not only effective against the sensitive strain, but are more potent against MDR-TB than antimycobacterial drugs used in therapy. The compounds showed low to moderate selectivity index values (SI) towards the bacteria, using MRC-5 cells (ATCC CCL-171) as mammalian cell model. Interaction with DNA was explored to get insight into the potential mechanism of action against the pathogen. No significant interaction was detected, allowing to discard this biomolecule as a potential molecular target. Compound 1 was identified as a hit compound (MIC90 2.23 μM; SI 4.4) to develop further chemical modifications in the search for new drugs.



DOI: 10.1016/j.jinorgbio.2021.111683
PMID: 34896768

43. **Molecular insights into the differential efflux mechanism of Rv1634 protein, a multidrug transporter of major facilitator superfamily in Mycobacterium tuberculosis.**

Proteins. 2022 Feb;90(2):566-578. doi: 10.1002/prot.26253. Epub 2021 Oct 19.

Singh G(1), Akhter Y(1).

Currently, multidrug-resistant tuberculosis (MDR-TB) is a public health crisis and a major health security threat globally. In Mycobacterium tuberculosis (Mtb), major facilitator superfamily (MFS) is the largest group of secondary active transporters. Along with the transport of their natural substrates, MFS proteins were involved in a drug efflux mechanism that ultimately lead to resistance against available anti-TB drugs in Mtb. In the present study, the three-dimensional structure model of an MFS protein, Rv1634, a probable multidrug transporter from Mtb, was generated using homology modeling. The

protein structure model was found in inward-open conformation having 14 transmembrane helices. In addition, a central transport channel was deduced across the protein, and a single binding pocket was identified halfway through the central cavity by structural alignment with the homologous protein structures. Further, Rv1634 protein was studied based on the differential structural behavior of apo and ligand-bound forms. All the protein systems were inserted into a phospholipid bilayer to characterize the conformational dynamics of the protein using molecular dynamics (MD) simulations. Detailed analysis of the MD trajectories showed the diverse substrate specificity of the binding pocket for the antibiotics that caused differential movement in the ciprofloxacin and norfloxacin, to which Mtb strains have now become resistant. The expulsion of the drugs outside the bacterial cell occurs through the alternating-access mechanism of N and C-terminal domains, which is intriguing and essential to the understanding the drug resistance mechanism in pathogenic bacteria.



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PMID: 34601761

44. **Strong Increase in Moxifloxacin Resistance Rate among Multidrug-Resistant Mycobacterium tuberculosis Isolates in China, 2007 to 2013.**

Microbiol Spectr. 2021 Dec 22;9(3):e0040921. doi: 10.1128/Spectrum.00409-21. Epub 2021 Dec 1.

Xia H(1), Zheng Y(1), Liu D(2), Wang S(1), He W(1), Zhao B(1), Song Y(1), Ou X(1), Zhou Y(1), van den Hof S(3), Cobelens F(4), Zhao Y(1).

We designed this study to determine the trend of moxifloxacin resistance among multidrug-resistant tuberculosis (MDR-TB) patients from 2007 to 2013 in China to inform the composition of multidrug-resistant/rifampicin-resistant tuberculosis (MDR/RR-TB) treatment regimens. We assessed moxifloxacin resistance among MDR-TB isolates collected in national drug resistance surveys in 2007 and 2013 that included 3,634 smear-positive and 7,206 culture-positive pulmonary tuberculosis patients, respectively. Moxifloxacin susceptibility was examined by a Mycobacterium growth indicator tube (MGIT) 960 for the 2007 isolates, and by the minimum inhibitory concentration (MIC) method for the 2013 isolates, at both breakpoints 0.5 and 2.0 μg/mL. Risk factors were explored through multivariable log-binominal regression analysis. Mutations in gyrA and gyrB for part of the isolates were also studied through sequencing. Of 401 MDR strains isolated in 2007, moxifiloxacin resistance could be determined for 319 (79.6%): 41 (12.9%)

and 10 (3.1%) were resistant at 0.5 and 2.0 μg/mL, respectively. Of 365 MDR strains isolated in 2013, 338 (92.6%) could be analyzed: 140 (41.4%) and 79 (23.4%) were resistant at 0.5 and 2.0 μg/mL. For patients in 2007, no characteristics were significantly associated with moxifloxacin resistance. For patients in 2013, patients aged ≥60 years (adjusted prevalence ratio [aPR], 1.46; 95% confidence interval [CI], 1.10 to 1.93) were more likely to have resistance at 0.5 μg/mL, whereas those residing in eastern China compared to those in central China had an increased risk of resistance at both 0.5 (aPR, 1.85; 95% CI, 1.38 to 2.48) and 2.0 μg/mL (aPR, 2.14; 95% CI, 1.35 to 3.40). Sequencing results were obtained for 245 and 266 MDR-TB isolates in 2007 and 2013, respectively. In total, 34 of 38 (89.5%) and 89 of 104 (85.6%) of 2007 and 2013 moxifloxacin-resistant (0.5 μg/mL) MDR-TB strains had mutations in the gyrA and gyrB gene, respectively. Asp94Gly was the most common mutation among 2007 (11 of 38, 28.9%) and 2013 isolates (24 of 104, 23.1%) and conferred high-level moxifloxacin resistance. Moxifloxacin resistance among MDR-TB patients in China increased from modest to high from 2007 to 2013. Moxifloxacin should be used carefully as a potentially effective drug for composing MDR/RR-TB regimens especially for elderly patients in China. Individual susceptibility testing especially rapid molecular-based assays should be conducted to confirm the susceptibility to moxifloxacin. IMPORTANCE China is one of the high-burden countries for multidrug-resistant/rifampicin-resistant tuberculosis (MDR/RR-TB). Moxifloxacin is one of the critical antituberculosis drugs for MDR/RR-TB treatment. Susceptibility to moxifloxacin is therefore very important to compose effective regimens and to provide protection against development of resistance of companion drugs such as bedaquiline and linezolid. There are, however, no nationally representative data on moxifloxacin resistance among MDR/RR-TB cases in China. Therefore, we assessed the resistance prevalence for moxifloxacin among MDR-TB strains isolated in national drug resistance surveys in 2007 and 2013 that covered 72 sites around the country. We demonstrate that the prevalence of moxifloxacin resistance in MDR-TB isolates increased from modest to high, which should prompt the national tuberculosis program to use moxifloxacin cautiously in second-line regimens to treat MDR/RR-TB unless susceptibility can be laboratory-confirmed.

DOI: 10.1128/Spectrum.00409-21
PMCID: PMC8635133
PMID: 34851179

45. **Single ascending dose safety, tolerability, and pharmacokinetic study of econazole in healthy volunteers.**

Expert Rev Anti Infect Ther. 2022 Jan 2:1-7. doi: 10.1080/14787210.2022.2016392. Online ahead of print.

Khera H(1), Pandey AK(1), Shafiq N(1), Khuller GK(2), Kondel Bhandari R(1), Panditrao A(1), Gamad N(1), Rohilla R(1), Bhattacharjee S(1), Murali N(1), Cvn H(1), Belavagi D(1), Mothsara C(1), Singh M(3), Sharma N(4), Behera D(5), Malhotra S(1).

INTRODUCTION: Econazole has been found efficacious as antitubercular in in vitro and in vivo animal studies. However, limited information is available for its safety and pharmacokinetics in humans. In our present study we have conducted single ascending dose, safety, and pharmacokinetic evaluation in healthy human volunteers with the purpose of enabling translation for tuberculosis.
METHODS: This study was conducted as a single-center, ascending-dose, placebo-controlled, double blind design. Three ascending dose were chosen (250 , 500 , and 1000 mg) to be administered as a single oral dose. The volunteers were screened for potential eligibility. Participants were randomized to receive either Econazole or Placebo in a 6:2 design. Safety assessments and pharmacokinetic evaluations were carried out for each cohort.
RESULTS: Econazole was found to be safe at all dose levels. No serious or severe adverse events occurred during the study. The AUC (0-∞) showed a response relationship with a value of 49 ± 3.47 h* µg/ml, 17. 86 ± 8.40 hr* µg/ml, 35.54 ± 13.94 hr* µg/ml for 250 mg, 500 mg, and 1000 mg, respectively.
CONCLUSION: Based on the findings of our study, a dose of 500 mg Econazole, once a day orally was considered as appropriate for further evaluation.

DOI: 10.1080/14787210.2022.2016392
PMID: 34913825

46. **Has the Time Come for Systematic Therapeutic Drug Monitoring of First-Line and WHO Group A Antituberculosis Drugs?**

Ther Drug Monit. 2022 Feb 1;44(1):133-137. doi: 10.1097/FTD.0000000000000948.

Lemaitre F(1)(2).

Tuberculosis (TB) is a major global health issue, with approximately 10 million people being infected each year, and is the leading cause of mortality from infectious disease, with 1.5 million deaths a year. Optimal TB treatment requires a combination of drugs for an adequate treatment duration owing to persistent organisms, hardly accessible infection sites, and a high risk of resistance selection. Long-term therapy increases the risk of patients' loss of adherence, adverse drug reactions, and drug-drug interactions, potentially leading to treatment failure. The high interpatient variability of TB drug exposure is another point eliciting interest in therapeutic drug monitoring

(TDM) to optimize treatment. Studies reporting clinically relevant exposure thresholds, which might be proposed as targets toward treatment personalization, are discussed. Practical TDM strategies have also been reported to circumvent issues related to delayed drug absorption and the need for multiple samples when evaluating the area under the curve of drug concentrations. The need for treatment individualization is further emphasized because of the development of multidrug-resistant TB or extensively drug-resistant TB. Finally, the willingness to shorten the treatment duration while maintaining success is also a driver for ensuring adequate exposure to TB drugs with TDM. The aim of the present review was to underline the role of TDM in drug-susceptible TB and World Health Organization group A TB drugs.



DOI: 10.1097/FTD.0000000000000948
PMID: 34857693

47. **A new treatment for drug-resistant tuberculosis in Ukraine.**

Lancet Infect Dis. 2022 Jan;22(1):23. doi: 10.1016/S1473-3099(21)00772-6.

Holt E.

DOI: 10.1016/S1473-3099(21)00772-6
PMID: 34953550 [Indexed for MEDLINE]

48. **Diagnostic Accuracy of Pyrazinamide Susceptibility Testing in Mycobacterium tuberculosis: A Systematic Review with Meta-Analysis.**

Microb Drug Resist. 2022 Jan;28(1):87-98. doi: 10.1089/mdr.2021.0048. Epub 2021 Sep 28.

Bagheri M(1), Pormohammad A(2), Fardsanei F(3), Yadegari A(4), Arshadi M(5), Deihim B(6), Hajikhani B(7), Turner RJ(2), Khalili F(1), Mousavi SMJ(7), Dadashi M(8), Goudarzi M(7), Dabiri H(7), Goudarzi H(7), Mirsaeidi M(9), Nasiri MJ(7).

Introduction: Pyrazinamide (PZA) susceptibility testing plays a critical role in determining the appropriate treatment regimens for multidrug-resistant tuberculosis. We conducted a systematic review and meta-analysis to evaluate the diagnostic accuracy of sequencing PZA susceptibility tests against culture-based susceptibility testing methods as the reference standard. Methods: We searched the MEDLINE/PubMed, Embase, and Web of Science databases for the relevant

records. The QUADAS-2 tool was used to assess the quality of the studies. Diagnostic accuracy measures (i.e., sensitivity and specificity) were pooled with a random-effects model. All statistical analyses were performed with Meta-DiSc (version 1.4, Cochrane Colloquium, Barcelona, Spain), STATA (version 14, Stata Corporation, College Station, TX), and RevMan (version 5.3, The Nordic Cochrane Centre, the Cochrane Collaboration, Copenhagen, Denmark) software. Results: A total of 72 articles, published between 2000 and 2019, comprising data for 8,701 isolates of Mycobacterium tuberculosis were included in the final analysis. The pooled sensitivity and specificity of the PZA sequencing test against all reference tests (the combination of BACTEC mycobacteria growth indicator tube 960 (MGIT 960), BACTEC 460, and proportion method) were 87% (95% CI: 85-88) and 94.7% (95% CI: 94-95). The positive likelihood ratio, negative likelihood ratio, diagnostic odds ratio, and the area under the curve estimates were found to be 12.0 (95% CI: 9.0-16.0), 0.17 (95% CI: 0.13-0.21), 106 (95% CI: 71-158), and 96%, respectively. Deek's test result indicated a low likelihood for publication bias (p = 0.01). Conclusions: Our analysis indicated that PZA sequencing may be used in combination with conventional tests due to the advantage of the time to result and in scenarios where culture tests are not feasible. Further work to improve molecular tests would benefit from the availability of standardized reference standards and improvements to the methodology.

DOI: 10.1089/mdr.2021.0048
PMID: 34582723

49. **Diagnostic yield of image-guided biopsy in patients with suspected infectious spondylodiscitis : a prospective study from a tuberculosis-endemic country.**

Bone Joint J. 2022 Jan;104-B(1):120-126. doi: 10.1302/0301-620X.104B1.BJJ-2021-0848.R2.

Kafle G(1), Garg B(1), Mehta N(1), Sharma R(2), Singh U(3), Kandasamy D(2), Das P(4), Chowdhury B(1).

AIMS: The aims of this study were to determine the diagnostic yield of image-guided biopsy in providing a final diagnosis in patients with suspected infectious spondylodiscitis, to report the diagnostic accuracy of various microbiological tests and histological examinations in these patients, and to report the epidemiology of infectious spondylodiscitis from a country where tuberculosis (TB) is endemic, including the incidence of drug-resistant TB. METHODS: A total of 284 patients with clinically and radiologically suspected infectious spondylodiscitis were prospectively recruited into the study. Image-guided biopsy of the vertebral lesion was performed and specimens were

sent for various microbiological tests and histological examinations. The final diagnosis was determined using a composite reference standard based on clinical, radiological, serological, microbiological, and histological findings. The overall diagnostic yield of the biopsy, and that for each test, was calculated in light of the final diagnosis.
RESULTS: The final diagnosis was tuberculous spondylodiscitis in 250 patients (88%) and pyogenic spondylodiscitis in 22 (7.8%). Six (2.1%) had a noninfectious condition-mimicking infectious spondylodiscitis, and six (2.1%) had no definite diagnosis and improved without specific treatment. The diagnosis was made by image-guided biopsy in 152 patients (56%) with infectious spondylodiscitis. Biopsy was contributory in identifying 132/250 patients (53%) with tuberculous spondylodiscitis, and 20/22 patients (91%) with pyogenic spondylodiscitis. Histological examination was the most sensitive diagnostic modality, followed by Xpert MTB/RIF assay.
CONCLUSION: Image-guided biopsy has a reasonably high diagnostic yield in patients with suspected infectious spondylodiscitis. A combination of histological examination, Xpert MTB/RIF assay, bacterial culture, and sensitivity provides high diagnostic accuracy in a country in which TB is endemic. Cite this article: Bone Joint J 2022;104-B(1):120-126.

DOI: 10.1302/0301-620X.104B1.BJJ-2021-0848.R2
PMID: 34969288 [Indexed for MEDLINE]

50. **Insights into transmission dynamics of Mycobacterium tuberculosis complex in Nepal.**

Trop Med Health. 2022 Jan 11;50(1):8. doi: 10.1186/s41182-022-00400-z.

Shah Y(1), Paudel S(2), Pandey K(3)(4), Gupta GP(5), Solo ES(6), Joshi J(7), Pant DK(8), Pandey BD(4)(9).

Tuberculosis (TB) is an infectious disease caused by Mycobacterium tuberculosis complex (MTBC) in humans and animals. Numbers of multi drug resistance TB (MDR-TB), extrapulmonary TB (EPTB) and zoonotic TB cases are increasingly being reported every year in Nepal posing a major public health problem. Therefore, the Government of Nepal should act immediately to strengthen the screening facilities across the country to be able to identify and treat the TB infected patients as well as detect zoonotic TB in animal species. Endorsement of One Health Act by the Government of Nepal is an opportunity to initiate the joint programs for TB surveillance among human and animal species using one health approach to reduce the TB burden in Nepal.

DOI: 10.1186/s41182-022-00400-z
PMCID: PMC8747996
PMID: 35012673

51. **Exploring disordered loops in DprE1 provides a functional site to combat drug-resistance in Mycobacterium strains.**

Eur J Med Chem. 2022 Jan 5;227:113932. doi: 10.1016/j.ejmech.2021.113932. Epub 2021 Oct 20.

Liu J(1), Dai H(2), Wang B(3), Liu H(4), Tian Z(5), Zhang Y(6).

As an anti-tuberculosis target, DprE1 contains two flexible loops (Loop I and Loop II) which have never been exploited for developing DprE1 inhibitors. Here Leu317 in Loop II was discovered as a new functional site to combat drug-resistance in Mycobacterium strains. Based on TCA1, LZDT1 was designed to optimize the hydrophobic interaction with Leu317. A subsequent biochemical and cellular assay displayed increased potency of LZDT1 in inhibiting DprE1 and killing drug-sensitive/-resistant Mycobacterium strains. The improved activity of LZDT1 and its analogue LZDT2 against multidrug resistant tuberculosis was particularly highlighted. For LZDT1, its enhanced interaction with Leu317 also impaired the drug-insensitivity of DprE1 caused by Cys387 mutation. A new nonbenzothiazole lead (LZDT10) with reduced Cys387-dependence was further produced by optimizing interactions with Leu317, improvement directions for LZDT10 were discussed as well. Our research underscores the value of potential functional sites in disordered loops, and affords a feasible way to develop these functional sites into opportunities for drug-resistance management.



DOI: 10.1016/j.ejmech.2021.113932
PMID: 34700267

52. **A novel ensemble based recommendation approach using network based analysis for identification of effective drugs for Tuberculosis.**

Math Biosci Eng. 2022 Jan;19(1):873-891. doi: 10.3934/mbe.2022040. Epub 2021 Nov 22.

Haldar R(1), Narayanan SJ(1).

Tuberculosis (TB) is a fatal infectious disease which affected millions of people worldwide for many decades and now with mutating drug resistant strains, it poses bigger challenges in treatment of the patients. Computational techniques might play a crucial role in rapidly developing new or modified anti-tuberculosis drugs which can tackle these mutating strains of TB. This research work applied a computational approach to generate a unique recommendation list of possible TB drugs as an alternate to a popular drug, EMB, by first securing an initial list of drugs from a popular online database, PubChem, and thereafter applying an ensemble of ranking mechanisms. As a novelty, both the pharmacokinetic properties and some network based attributes of the chemical structure of the drugs are considered for generating separate recommendation lists. The work also provides customized modifications on a popular and traditional ensemble ranking technique to cater to the specific dataset and requirements. The final recommendation list provides established chemical structures along with their ranks, which could be used as alternatives to EMB. It is believed that the incorporation of both pharmacokinetic and network based properties in the ensemble ranking process added to the effectiveness and relevance of the final recommendation.

DOI: 10.3934/mbe.2022040
PMID: 34903017

53. **Decreased Methylenetetrahydrofolate Reductase Activity Leads to Increased Sensitivity to para-Aminosalicylic Acid in Mycobacterium tuberculosis.**

Antimicrob Agents Chemother. 2022 Jan 18;66(1):e0146521. doi: 10.1128/AAC.01465-21. Epub 2021 Nov 15.

Yu JF(#)(1)(2), Xu JT(#)(1)(2), Yang SS(1), Gao MN(3), Si HR(1)(2), Xiong DY(1)(2), Gu J(1), Wu ZL(4), Zhou J(4), Deng JY(1)(5).

Tuberculosis (TB), caused by Mycobacterium tuberculosis, is one of the most fatal diseases in the world. Methylenetetrahydrofolate reductase (MTHFR) catalyzes the production of 5-methyltetrahydrofolate (5-CH3-THF), which is required for the de novo biosynthesis of methionine in bacteria. Here, we identified Rv2172c as an MTHFR in M. tuberculosis through in vitro and in vivo analyses and determined that the protein is essential for the in vitro growth of the bacterium. Subsequently, we constructed rv2172c R159N and L214A mutants in M. tuberculosis and found that these mutants were more sensitive to the antifolates para-aminosalicylic acid (PAS) and sulfamethoxazole (SMX). Combining biochemical and genetic methods, we found that rv2172c R159N or L214A mutation impaired methionine production, leading to increased susceptibility of M. tuberculosis to PAS, which was largely restored by adding exogenous methionine.

Moreover, overexpression of rv2172c in M. tuberculosis could increase methionine production and lead to PAS resistance. This research is the first to identify an MTHFR in M. tuberculosis and reveals that the activity of this enzyme is associated with susceptibility to antifolates. These findings have particular value for antitubercular drug design for the treatment of drug-resistant TB.

DOI: 10.1128/AAC.01465-21
PMID: 34780266

54. **Drug resistant tuberculosis in Afghanistan: We must continue to put people at the centre of treatment.**

BMJ. 2022 Jan 10;376:o46. doi: 10.1136/bmj.o46.

Mesic A.

DOI: 10.1136/bmj.o46
PMID: 35012958 [Indexed for MEDLINE]

55. **Treatment Outcomes of Patients with Multidrug-Resistant Tuberculosis: Concern to Bedaquiline: Authors' Reply.**

Tuberc Respir Dis (Seoul). 2022 Jan;85(1):98-99. doi: 10.4046/trd.2021.0135. Epub 2021 Sep 13.

Kang Y(1), Mok J(2)(3)(4).

DOI: 10.4046/trd.2021.0135
PMID: 34510868

56. **A case report of transmission and disease caused by Mycobacterium caprae and Mycobacterium bovis in Lima, Peru.**

BMC Infect Dis. 2021 Dec 20;21(1):1265. doi: 10.1186/s12879-021-06944-5.

Shrestha A(1), Picoy J(2), Torres A(3), Moore DA(4), Gilman RH(5)(6), Coronel J(7), Grandjean L(8)(9).

BACKGROUND: The Tuberculosis (TB) burden in Peru is significant with respect to both disease morbidity and mortality. Furthermore the recent diversification of farming enterprise to include a wide range of animal species has necessitated

the consideration of members of the Mycobacterium Tuberculosis Complex (MTBC) with the potential for zoonotic transmission. M. bovis and M. caprae, a lesser known member of the MTBC exhibit an exceptionally wide host spectrum in animals and are capable of causing disease in humans. M. bovis has a predictable resistance profile which includes resistance to pyrazinamide. Thus, failure to identify M. bovis as the causative agent in reported TB cases leads to higher levels of treatment failure and contributes to the transmission of drug-resistant TB.
CASE PRESENTATION: Reported here are the clinical presentations, investigations and treatment histories of two patients identified from a population level genotyping study in Lima, Peru that were at the time of treatment thought to be M. tuberculosis patients but in retrospect were spectated using whole genome sequencing as M. caprae and M. Bovis.
CONCLUSIONS: The cases reported here constitute convincing evidence that M. caprae and M. bovis are causative agents of TB infection in humans in Peru and underscore the importance of species-level MTBC member identification to effectively control and treat zoonotic TB. Furthermore these cases highlight the challenges of using clinical risk factors to identify cases of zoonotic TB in humans as their clinical presentation and transmission history is often difficult to distinguish from anthroponotic TB.



DOI: 10.1186/s12879-021-06944-5
PMCID: PMC8686613
PMID: 34930187 [Indexed for MEDLINE]

57. **A Review on Nuclear Imaging as a Promising Modality for Efficient Diagnosis of Tuberculosis.**

Curr Med Imaging. 2022;18(1):18-31. doi: 10.2174/1573405617666210707150811.

Rafique A(1), Rasheed R(2), Shamim S(3), Ijaz M(3), Murtaza G(4).

Tuberculosis (TB) is an infectious disease, which has been declared as a global health issue by the World Health Organization in 1993. Due to the complex pathophysiology of Mycobacterium tuberculosis, it remains a global threat. This article reviews the conventional diagnostic modalities for tuberculosis, their limitations to detect latent TB, multiple drug resistant-TB, human immunodeficiency virus co-infected TB lesions, and TB in children. Moreover, this review illustrates the importance of nuclear medicine imaging for early, non-invasive diagnosis of TB, to detect disease stages and to monitor therapy response. Single-photon emission computed tomography and positron emission

tomography with their particular radionuclides are now extensively being used for a thorough assessment of TB.



DOI: 10.2174/1573405617666210707150811
PMID: 34238164

58. **Cryo-EM structure of Mycobacterium tuberculosis 50S ribosomal subunit bound with clarithromycin reveals dynamic and specific interactions with macrolides.**

Emerg Microbes Infect. 2021 Dec 22:1-46. doi: 10.1080/22221751.2021.2022439. Online ahead of print.

Zhang W(1), Li Z(2)(3), Sun Y(4), Cui P(5), Liang J(6), Xing Q(1), Wu J(5), Xu Y(1), Zhang W(5), Zhang Y(5)(7), He L(1)(8), Gao N(2).

Tuberculosis (TB) is the leading infectious disease caused by Mycobacterium tuberculosis (Mtb). Clarithromycin (CTY), an analog of erythromycin (ERY), is more potent against multidrug-resistance (MDR) TB. ERY and CTY were previously reported to bind to the nascent polypeptide exit tunnel (NPET) near peptidyl transferase center (PTC), but the only available CTY structure in complex with D. radiodurans (Dra) ribosome could be misinterpreted due to resolution limitation. To date, the mechanism of specificity and efficacy of CTY for Mtb remains elusive since the Mtb ribosome-CTY complex structure is still unknown. In this study, we employed new sample preparation methods, and solved the Mtb ribosome-CTY complex structure at 3.3Å with cryo-EM technique, where the crucial gate site A2062 (E. coli numbering) is located at the CTY binding site within NPET. Two alternative conformations of A2062, a novel syn conformation as well as a swayed conformation bound with water molecule at interface, may play a role in coordinating the binding of specific drug molecules. The previously overlooked C-H hydrogen bond (H-bond) and π interaction may collectively contribute to the enhanced binding affinity. Together, our structure data provide a structural basis for the dynamic binding as well as the specificity of CTY, and propose an explanation of how a single methyl group in CTY improves its potency, which provides new evidence to reveal the previously unclear mechanism of translational modulation for future drug design and anti-TB therapy. Furthermore, our sample preparation method may facilitate drug discovery based on the complexes with low water solubility drugs by cryo-EM technique.

DOI: 10.1080/22221751.2021.2022439
PMID: 34935599

59. **Assessing the utility of the Xpert Mycobacterium tuberculosis/rifampin assay for analysis of bronchoalveolar lavage fluid in patients with suspected pulmonary tuberculosis.**

J Clin Lab Anal. 2022 Jan;36(1):e24154. doi: 10.1002/jcla.24154. Epub 2021 Dec 1.

Bai W(1), Liu L(2), Wu L(1), Chen S(3), Wu S(1), Wang Z(4), Xu K(1), Chi Q(5), Pan Y(6), Xu X(6).

BACKGROUND: There is limited research assessing the utility of the Xpert Mycobacterium tuberculosis/rifampin (MTB/RIF) assay for the analysis of bronchoalveolar lavage fluid (BALF) in Chinese patients with suspected pulmonary tuberculosis (PTB). Thus, our objective was to determine the diagnostic accuracy of the Xpert MTB/RIF assay and evaluate its utility for the determination of rifampicin resistance.
METHODS: We retrospectively analyzed BALF from 214 patients with suspected PTB between January 2018 and March 2019. Using mycobacterial culture or final clinical diagnosis as the reference standard, the diagnostic accuracy of the smear microscopy (SM), tuberculosis bacillus DNA (TB-DNA), Xpert MTB/RIF assay, and the determination of rifampicin resistance based on the Xpert MTB/RIF assay were compared.
RESULTS: As compared to mycobacterial culture, the sensitivity of the Xpert MTB/RIF assay, SM, and TB-DNA were 85.5% (74.2%-93.1%), 38.7% (26.6%-51.9%), and 67.7% (54.7%-79.1%), respectively. As compared to the final diagnosis, the specificity of the Xpert MTB/RIF assay, SM, and TB-DNA were 100.0% (95.9%-100.0%), 94.3% (87.1%-98.1%), and 98.9% (93.8%-100.0%), respectively. The sensitivity and specificity of the rifampicin resistance detection using the Xpert MTB/RIF assay were 100% and 98.0%, respectively, with liquid culture as the reference.
CONCLUSIONS: This study demonstrates that the analysis of BALF with the Xpert MTB/RIF assay provides a rapid and accurate tool for the early diagnosis of PTB. The accuracy of diagnosis was superior compared with the SM and TB-DNA. Moreover, Xpert is a quick and accurate method for the diagnosis of rifampicin-resistant tuberculosis and can also provide more effective guidance for the treatment of PTB or multidrug-resistant tuberculosis (MDR-TB).



DOI: 10.1002/jcla.24154
PMID: 34850984

60. **Cycloserine did not increase depression incidence or severity at standard dosing for MDR-TB.**

Eur Respir J. 2021 Dec 23:2102511. doi: 10.1183/13993003.02511-2021. Online ahead of print.

Tornheim JA(1), Udwadia ZF(2), Arora PR(3), Gajjar I(3), Gupte N(4)(5), Sharma S(3), Karane M(3), Sawant N(3), Kharat N(3), Blum AJ(6), Shivakumar SVBY(5), Mullerpattan JB(2), Pinto LM(2), Ashavaid TF(3), Gupta A(4)(7), Rodrigues C(8).

DOI: 10.1183/13993003.02511-2021
PMID: 34949698