Pub Med Open Access

1. Drug-resistant tuberculosis: the next sequence of events.

Lancet Microbe. 2024 Jan;5(1):e1. doi: 10.1016/S2666-5247(23)00402-0. Epub 2023 Dec 21.

The Lancet Microbe.

DOI: 10.1016/S2666-5247(23)00402-0
PMID: 38142710 [Indexed for MEDLINE]

2. Role for Linezolid in drug sensitive tuberculosis.

J Infect Public Health. 2024 Jan;17(1):172-174. doi: 10.1016/j.jiph.2023.11.012. Epub 2023 Nov 13.

Ramesh Kumar S(1), Narendran G(2), Padmapriyadarsini C(3).

Tuberculosis (TB) continues to be a global challenge. Reducing the duration of TB treatment for drug-sensitive TB (DSTB) has direct and distinct advantages. We ventured into the aspect of utilizing linezolid as a pivotal drug in shortening therapy in DSTB. Linezolid has gained prominence as it is faring well in resistant TB management. Only a few studies use the strategy of Linezolid in DS-TB but it seems a lucrative approach, the bactericidal effects have been reported favourably in the studies. There have been concerns about the potential adverse drug effects of Linezolid reported but clinical trials have demonstrated safety and tolerability when administered for shorter periods. If the safety and efficacy of giving Linezolid for a shorter period along with standard drugs for DSTB is established it could lead to newer avenues using Linezolid for shortening the duration of treatment for DSTB as an alternative to treat DSTB.

DOI: 10.1016/j.jiph.2023.11.012
PMID: 38039860 [Indexed for MEDLINE]

Conflict of interest statement: Declaration of Competing Interest The authors declare nil conflict of interest.

3. Multidrug-resistant tuberculosis in Iran: a multicenter study.

Monaldi Arch Chest Dis. 2024 Jan 12. doi: 10.4081/monaldi.2024.2844. Online ahead of print.

Khelghati F(1), Nasirpour Seilakhori F(2), Goudarzi M(3), Malekloo S(4), Shahidi Bonjar AH(5), Goudarzi H(6), Nasiri MJ(7).

The worldwide incidence of multi-drug-resistant tuberculosis (MDR-TB) is rapidly increasing, and it has emerged as a pressing public health issue in Iran. Nevertheless, there is a scarcity of up-to-date research on the prevalence of MDR-TB in individuals with pulmonary TB in the country. In this cross-sectional study, we gathered a total of 1216 respiratory samples, each corresponding to a unique patient, from five distinct regional TB laboratories in Iran. We identified clinical isolates as Mycobacterium tuberculosis using the IS6110-based PCR assay and Xpert MTB/RIF. Drug susceptibility testing (DST) was conducted using the conventional proportion method. Out of the collected specimens, 448 tested positive for M. tuberculosis. Among these isolates, 445 (99.4%) exhibited susceptibility to the tested drugs, while 3 (0.6%) were found to be MDR. The findings from this recent study indicate that the prevalence of MDR in Iran stands at 0.6%. The absence of recently approved treatment protocols in various regions of Iran, along with inadequately equipped laboratories lacking DST capabilities, could contribute significantly to the rise in TB/MDR-TB prevalence in Iran. Therefore, the implementation of enhanced treatment management strategies and the adoption of innovative technologies are essential steps towards improving the current situation.

DOI: 10.4081/monaldi.2024.2844
PMID: 38214397

4. Chinese expert consensus on imaging diagnosis of drug-resistant pulmonary tuberculosis.

Quant Imaging Med Surg. 2024 Jan 3;14(1):1039-1060. doi: 10.21037/qims-23-1223. Epub 2023 Oct 25.

Xu CJ(#)(1), Lu PX(#)(2), Li CH(#)(3), He YL(#)(4), Fang WJ(#)(5), Xie RM(6), Jin GQ(7), Lu YB(8), Zheng QT(2), Zheng GP(9), Lv SX(3), Huang H(9), Li L(10), Ren M(10), Shi YX(11), Wen XN(12), Li L(13), Wei FJ(9), Hou DL(14), Lv Y(14), Shan F(11), Wu ZC(15), Hu ZL(16), Zhang XR(17), Liu DX(18), Shi WY(11), Li HR(5), Zhang N(19), Song M(5), Zhang X(20), Deng YY(21), Li J(22), Liu Q(23), Li D(24), Zhao L(25), Chen BD(26), Shi YB(25), Jiang FL(27), Tang X(4), Wu LJ(28), Ma W(29), Xu XY(30), Li HJ(10).

Tuberculosis (TB) remains one of the major infectious diseases in the world with

a high incidence rate. Drug-resistant tuberculosis (DR-TB) is a key and difficult challenge in the prevention and treatment of TB. Early, rapid, and accurate diagnosis of DR-TB is essential for selecting appropriate and personalized treatment and is an important means of reducing disease transmission and mortality. In recent years, imaging diagnosis of DR-TB has developed rapidly, but there is a lack of consistent understanding. To this end, the Infectious Disease Imaging Group, Infectious Disease Branch, Chinese Research Hospital Association; Infectious Diseases Group of Chinese Medical Association of Radiology; Digital Health Committee of China Association for the Promotion of Science and Technology Industrialization, and other organizations, formed a group of TB experts across China. The conglomerate then considered the Chinese and international diagnosis and treatment status of DR-TB, China's clinical practice, and evidence-based medicine on the methodological requirements of guidelines and standards. After repeated discussion, the expert consensus of imaging diagnosis of DR-PB was proposed. This consensus includes clinical diagnosis and classification of DR-TB, selection of etiology and imaging examination [mainly X-ray and computed tomography (CT)], imaging manifestations, diagnosis, and differential diagnosis. This expert consensus is expected to improve the understanding of the imaging changes of DR-TB, as a starting point for timely detection of suspected DR-TB patients, and can effectively improve the efficiency of clinical diagnosis and achieve the purpose of early diagnosis and treatment of DR-TB.

DOI: 10.21037/qims-23-1223
PMCID: PMC10784038
PMID: 38223121

Conflict of interest statement: Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-23-1223/coif). The authors have no conflicts of interest to declare.

5. Mycobacterium tuberculosis: immune response, biomarkers, and therapeutic intervention.

MedComm (2020). 2024 Jan 6;5(1):e419. doi: 10.1002/mco2.419. eCollection 2024 Jan.

Zhuang L(1)(2), Yang L(2), Li L(2), Ye Z(2), Gong W(1).

Although tuberculosis (TB) is an infectious disease, the progression of the

disease following Mycobacterium tuberculosis (MTB) infection is closely associated with the host's immune response. In this review, a comprehensive analysis of TB prevention, diagnosis, and treatment was conducted from an immunological perspective. First, we delved into the host's immune response mechanisms against MTB infection as well as the immune evasion mechanisms of the bacteria. Addressing the challenges currently faced in TB diagnosis and treatment, we also emphasized the importance of protein, genetic, and immunological biomarkers, aiming to provide new insights for early and personalized diagnosis and treatment of TB. Building upon this foundation, we further discussed intervention strategies involving chemical and immunological treatments for the increasingly critical issue of drug-resistant TB and other forms of TB. Finally, we summarized TB prevention, diagnosis, and treatment challenges and put forward future perspectives. Overall, these findings provide valuable insights into the immunological aspects of TB and offer new directions toward achieving the WHO's goal of eradicating TB by 2035.

DOI: 10.1002/mco2.419
PMCID: PMC10771061
PMID: 38188605

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

6. A four-drug standardized short regimen for highly resistant TB in South-West Nigeria.

Int Health. 2024 Jan 2;16(1):123-125. doi: 10.1093/inthealth/ihad023.

Fadeyi MO(1), Decroo T(2), Ortuño-Gutiérrez N(3), Ahmed B(1), Jinadu A(1), El-Tayeb O(3), Adebola W(4), Kehinde A(5), Lynen L(2), Gils T(2).

BACKGROUND: Patients with TB resistant to rifampicin (Rr-TB), and those with additional resistance to fluoroquinolones (pre-XDR-TB), should be treated with bedaquiline-pretomanid-linezolid-moxifloxacin and bedaquiline-pretomanid-linezolid, respectively. However, pretomanid is not yet widely available.
METHODS: This is a pragmatic prospective single-arm study investigating the efficacy and safety of 9 mo of bedaquiline-delamanid-linezolid-clofazimine in patients with pre-XDR-TB or Rr-TB unresponsive to Rr-TB treatment in Nigeria.
RESULTS: From January 2020 to June 2022, 14 of 20 patients (70%) successfully completed treatment, five died and one was lost-to-follow-up. No one experienced

a treatment-emergent grade three/four event. Treatment success was higher compared with global pre-XDR-TB treatment outcomes.
CONCLUSIONS: While pretomanid is unavailable, highly resistant TB can be treated with bedaquiline-delamanid-linezolid-clofazimine.

DOI: 10.1093/inthealth/ihad023
PMCID: PMC10759290
PMID: 37026448 [Indexed for MEDLINE]

Conflict of interest statement: None declared.

7. Whole genome sequencing of drug-resistant Mycobacterium tuberculosis isolates in Victoria, Australia.

Int J Infect Dis. 2024 Jan;138:46-53. doi: 10.1016/j.ijid.2023.11.010. Epub 2023 Nov 14.

Dorji T(1), Horan K(2), Sherry NL(3), Tay EL(4), Globan M(5), Viberg L(5), Bond K(6), Denholm JT(7), Howden BP(8), Andersson P(3).

OBJECTIVES: Whole genome sequencing (WGS) can identify clusters, transmission patterns, and drug resistance mutations. This is important in low-burden settings such as Australia, as it can assist in efficient contact tracing and surveillance.
METHODS: We conducted a retrospective cohort study using WGS from 155 genomically defined drug-resistant Mycobacterium tuberculosis (DR-TB) isolates collected between 2018-2021 in Victoria, Australia. Bioinformatic analysis was performed to identify resistance-conferring mutations, lineages, clusters and understand how local sequences compared with international context.
RESULTS: Of the 155 sequences, 42% were identified as lineage 2 and 35% as lineage 1; 65.8% (102/155) were isoniazid mono-resistant, 8.4% were multi-drug resistant TB and 5.8% were pre-extensively drug-resistant / extensively drug-resistant TB. The most common mutations were observed in katG and fabG1 genes, especially at Ser315Thr and fabG1 -15 C>T for first-line drugs. Ser450Leu was the most frequent mutation in rpoB gene. Phylogenetic analysis confirmed that Victorian DR-TB were associated with importation events. There was little evidence of local transmission with only five isolate pairs.
CONCLUSION: Isoniazid-resistant TB is the commonest DR-TB in Victoria, and the mutation profile is similar to global circulating DR-TB. Most cases are diagnosed among migrants with limited transmission. This study highlights the

value of WGS in identification of clusters and resistance-conferring mutations. This information is crucial in supporting disease mitigation and treatment strategies.

DOI: 10.1016/j.ijid.2023.11.010
PMID: 37967715 [Indexed for MEDLINE]

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

8. Burden of drug-resistant tuberculosis among contacts of index cases: a protocol for a systematic review.

BMJ Open. 2024 Jan 9;14(1):e074364. doi: 10.1136/bmjopen-2023-074364.

Akalu TY(1)(2)(3), Clements ACA(3)(4), Gebreyohannes EA(3)(5), Wolde HF(6)(2)(3), Shiferaw FW(7), Alene KA(2)(3).

INTRODUCTION: People having close contact with drug-resistant tuberculosis (DR-TB) patients are at increased risk of contracting and developing the disease. However, no comprehensive review has been undertaken to estimate the burden of DR-TB among contacts of DR-TB patients. Therefore, the current systematic review will quantify the prevalence and incidence of DR-TB among contacts of DR-TB patients.
METHOD AND ANALYSIS: Systematic searches will be conducted in Medline, Embase, Web of Science, Scopus, Cochrane Central Register of Controlled trials (CENTRAL) and Cumulative Index to Nursing and Allied Health Literature (CINHAL) databases. The search will be conducted without restrictions on time, language and geography. A random-effects meta-analysis will be conducted for effect estimates. The pooled prevalence and incidence of DR-TB will be compared between people with and without contact with DR-TB patients. The presence of heterogeneity between studies will be assessed by Higgins I2 statistics. Subgroup analysis will be conducted to determine the source of heterogeneity. The risk of bias will be assessed using a visual inspection of the funnel plot and Egger's regression test statistics. Trim and fill analysis will be done in the presence of publication bias. A sensitivity analysis will be conducted by trimming low-quality studies. The systematic review will be reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol guidelines.
ETHICS AND DISSEMINATION: Ethical approval will not be required for this study as it will be a systematic review and meta-analysis based on previously

published evidence. The findings of the systematic review will be presented at scientific conferences and published in scientific journals.
PROTOCOL REGISTRATION: The protocol is published in PROSPERO with registration number CRD42023390339.

DOI: 10.1136/bmjopen-2023-074364
PMID: 38195168 [Indexed for MEDLINE]

Conflict of interest statement: Competing interests: None declared.

9. Second-line antituberculosis drug exposure thresholds predictive of adverse events in multidrug-resistant tuberculosis treatment.

Int J Infect Dis. 2024 Jan 3;140:62-69. doi: 10.1016/j.ijid.2024.01.001. Online ahead of print.

Wang S(1), Forsman LD(2), Xu C(3), Zhang H(1), Zhu Y(1), Shao G(1), Wang S(1), Cao J(1), Xiong H(1), Niward K(4), Schön T(5), Bruchfeld J(2), Zhu L(6), Alffenaar JW(7), Hu Y(8).

OBJECTIVES: This study aimed to investigate the association between drug exposure and adverse events (AEs) during the standardized multidrug-resistant tuberculosis (MDR-TB) treatment, as well as to identify predictive drug exposure thresholds.
METHODS: We conducted a prospective, observational multicenter study among participants receiving standardized MDR-TB treatment between 2016 and 2019 in China. AEs were monitored throughout the treatment and their relationships to drug exposure (e.g., the area under the drug concentration-time curve from 0 to 24 h, AUC0-24 h) were analyzed. The thresholds of pharmacokinetic predictors of observed AEs were identified by boosted classification and regression tree (CART) and further evaluated by external validation.
RESULTS: Of 197 study participants, 124 (62.9%) had at least one AE, and 15 (7.6%) experienced serious AEs. The association between drug exposure and AEs was observed including bedaquiline, its metabolite M2, moxifloxacin and QTcF prolongation (QTcF >450 ms), linezolid and mitochondrial toxicity, cycloserine and psychiatric AEs. The CART-derived thresholds of AUC0-24 h predictive of the respective AEs were 3.2 mg·h/l (bedaquiline M2); 49.3 mg·h/l (moxifloxacin); 119.3 mg·h/l (linezolid); 718.7 mg·h/l (cycloserine).
CONCLUSIONS: This study demonstrated the drug exposure thresholds predictive of AEs for key drugs against MDR-TB treatment. Using the derived thresholds will

provide the knowledge base for further randomized clinical trials of dose adjustment to minimize the risk of AEs.

DOI: 10.1016/j.ijid.2024.01.001
PMID: 38176643

10. Global adoption of 6-month drug-resistant TB regimens: Projected uptake by 2026.

PLoS One. 2024 Jan 5;19(1):e0296448. doi: 10.1371/journal.pone.0296448. eCollection 2024.

Gupta A(1), Juneja S(1), Babawale V(2), Rustam Majidovich N(3), Ndjeka N(4), Thi Mai Nguyen P(5), Nargiza Nusratovna P(6), Robert Omanito D(7), Tiara Pakasi T(8), Terleeva Y(9), Toktogonova A(10), Waheed Y(11), Myint Z(12), Yanlin Z(13), Sahu S(14).

BACKGROUND: The WHO has issued a call to action urging countries to accelerate the rollout of new WHO-recommended shorter all-oral treatment regimens for drug-resistant TB (DR-TB), which remains a public-health crisis. The all-oral, 6-month BPaL/M regimen comprises 3-4 drugs: pretomanid used in combination with bedaquiline and linezolid, with or without moxifloxacin. This regimen has been recommended by the WHO for use in DR-TB patients instead of ≥9-month (up to 24-month) regimens. This study aims to project this regimen's use, along with its components bedaquiline, pretomanid and linezolid, and other treatments for DR-TB globally through 2026. It is intended to guide global health stakeholders in planning and budgeting for DR-TB interventions. Projected usage could help estimate cost of the individual components of DR-TB regimens over time.
METHODS: Semi-structured interviews were conducted with national TB programme participants in key countries to gather intelligence on established plans and targets for use of various DR-TB treatment regimens from 2023 to 2026. These data informed development of projections for the global use of regimens and drugs.
RESULTS: Consistent global growth in the use of shorter regimens in DR-TB treatment was shown: BPaLM reaching 126,792 patients, BPaL reaching 43,716 patients, and the 9-11-month all-oral bedaquiline-based regimen reaching 13,119 patients by 2026. By 2026, the longer all-oral regimen is projected to be used by 19,262 patients, and individualised treatment regimens by 15,344 patients.
CONCLUSION: The study shows BPaL/M will be used in majority of DR-TB patients by 2024, reaching 78% by 2026. However, national efforts to scale-up, case-finding, monitoring, drug-susceptibility testing, and implementation of new treatments will be essential for ensuring they are accessible to all eligible patients in

the coming years and goals for ending TB are met. There is an urgent need to engage communities in capacity building and demand generation.

DOI: 10.1371/journal.pone.0296448
PMCID: PMC10769048
PMID: 38180980 [Indexed for MEDLINE]

Conflict of interest statement: Authors, Aastha Gupta and Sandeep Juneja, are employed by TB Alliance, the non-profit product development partnership that developed pretomanid and the BPaL regimen for the treatment of drug-resistant tuberculosis. Author, Suvanand Sahu, serves on the Access Advisory Committee (an unpaid role) for TB Alliance, the non-profit product development partnership that developed pretomanid and the BPaL regimen for the treatment of drug-resistant tuberculosis. This does not alter our adherence to PLOS ONE policies on sharing data and materials.

11. Rapid detection of drug-resistant Mycobacterium tuberculosis by Modified MODS assay suitable for resource-poor settings.

PLoS Negl Trop Dis. 2024 Jan 4;18(1):e0011852. doi: 10.1371/journal.pntd.0011852. eCollection 2024 Jan.

Fomda BA(1), Bashir G(1), Baqal S(1), Mir YB(1), Ali R(1), Khan AH(1), Khan A(1), Bashir A(2), Chuloo GM(3).

BACKGROUND: Cross contamination and biosafety are concerns with the microscopic observation drug susceptibility assay. To address these issues, we modified the MODS technique in the current study.
METHODOLOGY/PRINCIPAL FINDINGS: Two hundred and seventy-five samples were processed on LJ media and drug susceptibility was performed by the Indirect agar proportion method. A modified MODS test was done in tissue culture bottles. GenoType MTBDRplus assay was performed to detect the resistance and mutational pattern associated with the resistances. Sensitivity, specificity, positive predictive value, and negative predictive value for the detection of tuberculosis by modified MODS were 97.44%, 80.00%, 97.44%, and 80.00% respectively. The perfect agreement was seen between modified MODS and the Indirect agar proportion method for drug susceptibility testing of isoniazid (kappa = 0.923) and rifampicin (kappa = 1). The contamination rate, cost and TAT

for modified MODS were less as compared to the solid media. In the case of MDR-TB isolates S531L (66.66%) was the most prevalent mutation in the rpoB gene followed by S315T2 mutation (58.33%) and T8C (41.66%) in katG and inhA gene respectively. In hetero-resistant strains, C-15T mutation (37.50%) was the most common followed by A-16G (12.50%) in the inhA gene. In INH mono-resistant strains only two mutations were observed i.e., S-315T1(50%) and C-15T (50%) in the katG and inhA genes respectively.
CONCLUSIONS/SIGNIFICANCE: Modified MODS proved to be cost-effective and user-friendly, with minimal risk to the handler and no cross-contamination between samples were observed. Hence, it can be used in low-income countries for early detection of tuberculosis and its resistance.

DOI: 10.1371/journal.pntd.0011852
PMCID: PMC10766176
PMID: 38175831 [Indexed for MEDLINE]

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

12. Pharmacokinetics and cardiac safety of clofazimine in children with rifampicin-resistant tuberculosis.

Antimicrob Agents Chemother. 2024 Jan 10;68(1):e0079423. doi: 10.1128/aac.00794-23. Epub 2023 Dec 19.

Ali AM(1)(2), P Solans B(1), Hesseling AC(3), Winckler J(3), Schaaf HS(3), Draper HR(3), van der Laan L(3), Hughes J(3), Fourie B(3), Nielsen J(4), Wiesner L(5), Garcia-Prats AJ(#)(3)(6), Savic RM(#)(1).

Clofazimine is recommended for the treatment of rifampicin-resistant tuberculosis (RR-TB), but there is currently no verified dosing guideline for its use in children. There is only limited safety and no pharmacokinetic (PK) data available for children. We aimed to characterize clofazimine PK and its relationship with QT-interval prolongation in children. An observational cohort study of South African children <18 years old routinely treated for RR-TB with a clofazimine-containing regimen was analyzed. Clofazimine 100 mg gelatin capsules were given orally once daily (≥20 kg body weight), every second day (10 to <20 kg), or thrice weekly (<10 kg). PK sampling and electrocardiograms were

completed pre-dose and at 1, 4, and 10 hours post-dose, and the population PK and Fridericia-corrected QT (QTcF) interval prolongation were characterized. Fifty-four children contributed both PK and QTcF data, with a median age (2.5th-97.5th centiles) of 3.3 (0.5-15.6) years; five children were living with HIV. Weekly area under the time-concentration curve at steady state was 79.1 (15.0-271) mg.h/L compared to an adult target of 60.9 (56.0-66.6) mg.h/L. Children living with HIV had four times higher clearance compared to those without. No child had a QTcF ≥500 ms. A linear concentration-QTcF relationship was found, with a drug effect of 0.05 (0.027, 0.075) ms/µg/L. In some of the first PK data in children, we found clofazimine exposure using an off-label dosing strategy was higher in children versus adults. Clofazimine concentrations were associated with an increase in QTcF, but severe prolongation was not observed. More data are required to inform dosing strategies in children.

DOI: 10.1128/aac.00794-23
PMCID: PMC10777824
PMID: 38112526 [Indexed for MEDLINE]

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

13. The emerging threat of fluroquinolone-, bedaquiline-, and linezolid-resistant Mycobacterium tuberculosis in China: Observations on surveillance data.

J Infect Public Health. 2024 Jan;17(1):137-142. doi: 10.1016/j.jiph.2023.11.018. Epub 2023 Nov 21.

Li S(1), Tan Y(2), Deng Y(3), Bai G(4), Huang M(5), Shang Y(1), Wang Y(1), Xue Z(1), Zhang X(1), Wang W(1), Pan J(6), Pang Y(7).

BACKGROUND: Drug-resistant tuberculosis (TB), especially multidrug-resistant tuberculosis (MDR-TB), constitutes a major obstacle to fulfill end TB strategy globally. Although fluoroquinolones (FQs), linezolid (LZD) and bedaquiline (BDQ) were classified as Group A drugs for MDR-TB treatment, our knowledge of the prevalence of TB which were resistant to Group A drugs in China is quite limited.
METHODS: In this study, we conducted a prospective multicenter surveillance study in China to determine the proportion of TB patients that were resistant to Group A drugs. A total of 1877 TB patients were enrolled from 2022 at four TB specialized hospitals. The drug susceptibility of isolated strains was conducted using the MGIT 960 system and the molecular mechanisms conferring drug resistance were investigated by Sanger sequencing.
RESULTS: 12.9% of isolates were resistant to levofloxacin (LFX), 13.2% were resistant to moxifloxacin (MOX), 0.2% were resistant to bedaquiline (BDQ), and

0.8% were resistant to linezolid (LZD). Totally, 14.0% and 0.4% were classified as multidrug resistant- (MDR-) and extensively drug resistant- (XDR-) TB. The drug resistance was more common in retreated TB cases compared to new cases. In addition, 70.0% of fluoroquinolone (FQ)-resistant isolates harbored mutations in the gyrA and gyrB gene. By contrast, the common drug-resistant mutations were only found in 50% BDQ-resistant and 20% LZD-resistant isolates.
CONCLUSIONS: Our data demonstrate that approximate half of MDR -TB patients are resistant to fluoroquinolones, with extremely low prevalence of initial BDQ and LZD resistance. Findings from this study provide important implications for the current management of MDR-TB patients.

DOI: 10.1016/j.jiph.2023.11.018
PMID: 38000314 [Indexed for MEDLINE]

Conflict of interest statement: Declaration of Competing Interest We have no conflict of interest to declare.

14. Spermine enhances the activity of anti-tuberculosis drugs.

Microbiol Spectr. 2024 Jan 11;12(1):e0356823. doi: 10.1128/spectrum.03568-23. Epub 2023 Dec 14.

Sao Emani C(1), Reiling N(1)(2).

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This is the first study that attempted to demonstrate the mechanisms of reactive oxygen species (ROS) generation by spermine (Spm) in Mycobacterium tuberculosis (M.tb). Furthermore, this is the first study to demonstrate that it is able to enhance the activity of currently available and World Health Organization (WHO)-approved tuberculosis (TB) drugs. Spermine can easily be obtained since it is already found in our diet. Moreover, as opposed to conventional antibiotics, it is less toxic to humans since it is found in millimolar concentrations in the body. Finally, with the difficulty of curing TB with conventional antibiotics, this study suggests that less toxic molecules, such as Spm, could in a long-term perspective be incorporated in a TB regimen to boost the treatment.

DOI: 10.1128/spectrum.03568-23
PMCID: PMC10782994
PMID: 38095461 [Indexed for MEDLINE]

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

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

Emerg Microbes Infect. 2024 Dec;13(1):2302837. doi: 10.1080/22221751.2024.2302837. Epub 2024 Jan 22.

Li M(1), Zhang Y(2)(3)(4), Wu Z(2)(3), Jiang Y(2)(3), Sun R(1), Yang J(5), Li J(2)(3), Lin H(1), Zhang R(1), Jiang Q(6), Wang L(2)(3), Wu X(5), Yu F(5), Yuan J(7), Yang C(1)(7), Shen X(2)(3).

Fluoroquinolones (FQ) are essential for the treatment of multidrug-resistant tuberculosis (MDR-TB). The FQ resistance (FQ-R) rate in MDR-TB in China and its risk factors remain poorly understood. We conducted a retrospective, population-based genomic epidemiology study of MDR-TB patients in Shanghai, China, from 2009 to 2018. A genomic cluster was defined as strains with genetic distances ≤ 12 single nucleotide polymorphisms. The transmitted FQ-R was defined as the same FQ resistance-conferring mutations shared by ≥ 2 strains in a genomic cluster. We used multivariable logistic regression analysis to identify the risk factors for drug resistance. Among the total 850 MDR-TB patients included in the study, 72.8% (619/850) were male, the median age was 39 (interquartile range 28, 55) years, 52.7% (448/850) were migrants, and 34.5% (293/850) were previously treated patients. Most of the MDR-TB strains belong to the Beijing lineage (91.7%, 779/850). Overall, the genotypic resistance rate of FQ was 34.7% (295/850), and 47.1% (139/295) FQ-R patients were in genomic clusters, of which 98 (33.2%, 98/295) were presumed as transmitted FQ-R. Patients with treatment-naïve (aOR = 1.84; 95% CI: 1.09, 3.16), diagnosed in a district-level hospital (aOR = 2.69; 95% CI: 1.56, 4.75), and streptomycin resistance (aOR = 3.69; 95% CI: 1.65, 9.42) were significantly associated with the transmission of FQ-R. In summary, the prevalence of FQ-R among MDR-TB patients was high in Shanghai, and at least one-third were transmitted. Enforced interventions including surveillance of FQ drug susceptibility testing and screening among MDR-TB before initiation of treatment were urgently needed.

DOI: 10.1080/22221751.2024.2302837
PMID: 38205528 [Indexed for MEDLINE]

16. Effect of mixed Mycobacterium tuberculosis infection on rapid molecular diagnostics among patients starting MDR-TB treatment in Uganda.

BMC Infect Dis. 2024 Jan 10;24(1):70. doi: 10.1186/s12879-023-08968-5.

Komakech K(1), Nakiyingi L(2), Fred A(3), Achan B(1), Joloba M(3), Kirenga BJ(4), Ssengooba W(5)(6).

Update of
Res Sq. 2023 Sep 28;:

BACKGROUND: Mixed M. tuberculosis (MTB) infection occurs when one is infected with more than one clonally distinct MTB strain. This form of infection can assist MTB strains to acquire additional mutations, facilitate the spread of drug-resistant strains, and boost the rate of treatment failure. Hence, the presence of mixed MTB infection could affect the performance of some rapid molecular diagnostic tests such as Line Probe Assay (LPA) and GeneXpert MTB/RIF (Xpert) assays.
METHODS: This was a cross-sectional study that used sputum specimens collected from participants screened for STREAM 2 clinical trial between October 2017 and October 2019. Samples from 62 MTB smear-positive patients and rifampicin-resistant patients from peripheral health facilities were processed for Xpert and LPA as screening tests for eligibility in the trial. From November 2020, processed stored sputum samples were retrieved and genotyped to determine the presence of mixed-MTB strain infection using a standard 24-locus Mycobacterial Interspersed Repetitive Unit-Variable Number Tandem-Repeat (MIRU-VNTR). Samples with at least 20/24 MIRU-VNTR loci amplified were considered for analysis. Agar proportional Drug Susceptibility Test (DST) was performed on culture isolates of samples that had discordant results between LPA and Xpert. The impact of the presence of mixed-MTB strain on Xpert and LPA test interpretation was analyzed.
RESULTS: A total of 53/62 (85%) samples had analyzable results from MIRU-VNTR. The overall prevalence of mixed-MTB infection was 5/53 (9.4%). The prevalence was highest among male's 3/31 (9.7%) and among middle-aged adults, 4/30 (33.3%). Lineage 4 of MTB contributed 3/5 (60.0%) of the mixed-MTB infection prevalence. Having mixed MTB strain infection increased the odds of false susceptible Xpert test results (OR 7.556, 95% CI 0.88-64.44) but not for LPA. Being HIV-positive (P = 0.04) independently predicted the presence of mixed MTB infection.
CONCLUSIONS: The presence of mixed-MTB strain infection may affect the performance of the GeneXpert test but not for LPA. For patients with high pre-test probability of rifampicin resistance, an alternative rapid method such as LPA should be considered.

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PMCID: PMC10782568
PMID: 38200467 [Indexed for MEDLINE]

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

17. Differences in pulmonary nodular consolidation and pulmonary cavity among drug-sensitive, rifampicin-resistant and multi-drug resistant tuberculosis patients: the Guangzhou computerized tomography study.

Quant Imaging Med Surg. 2024 Jan 3;14(1):1010-1021. doi: 10.21037/qims-23-694. Epub 2023 Nov 20.

Fang WJ(#)(1), Tang SN(#)(2), Liang RY(1), Zheng QT(3), Yao DQ(2), Hu JX(4), Song M(1), Zheng GP(5), Rosenthal A(6), Tartakovsky M(6), Lu PX(3), Wáng YXJ(2).

BACKGROUND: Pulmonary nodular consolidation (PN) and pulmonary cavity (PC) may represent the two most promising imaging signs in differentiating multidrug-resistant (MDR)-pulmonary tuberculosis (PTB) from drug-sensitive (DS)-PTB. However, there have been concerns that literature described radiological feature differences between DS-PTB and MDR-PTB were confounded by that MDR-PTB cases tend to have a longer history. This study seeks to further clarify this point.
METHODS: All cases were from the Guangzhou Chest Hospital, Guangzhou, China. We retrieved data of consecutive new MDR cases [n=46, inclusive of rifampicin-resistant (RR) cases] treated during the period of July 2020 and December 2021, and according to the electronic case archiving system records, the main PTB-related symptoms/signs history was ≤3 months till the first computed tomography (CT) scan in Guangzhou Chest Hospital was taken. To pair the MDR-PTB cases with assumed equal disease history length, we additionally retrieved data of 46 cases of DS-PTB patients. Twenty-two of the DS patients and 30 of the MDR patients were from rural communities. The first CT in Guangzhou Chest Hospital was analysed in this study. When the CT was taken, most cases had anti-TB drug treatment for less than 2 weeks, and none had been treated for more than 3 weeks.
RESULTS: Apparent CT signs associated with chronicity were noted in 10 cases in the DS group (10/46) and 9 cases in the MDR group (10/46). Thus, the overall disease history would have been longer than the assumed <3 months. Still, the history length difference between DS patients and MDR patients in the current study might not be substantial. The lung volume involvement was 11.3%±8.3% for DS cases and 8.4%±6.6% for MDR cases (P=0.022). There was no statistical

difference between DS cases and MDR cases both in PN prevalence and in PC prevalence. For positive cases, MDR cases had more PN number (mean of positive cases: 2.63 vs. 2.28, P=0.38) and PC number (mean of positive cases: 2.14 vs. 1.38, P=0.001) than DS cases. Receiver operating characteristic curve analysis shows, PN ≥4 and PC ≥3 had a specificity of 86% (sensitivity 25%) and 93% (sensitivity 36%), respectively, in suggesting the patient being a MDR cases. CONCLUSIONS: A combination of PN and PC features allows statistical separation of DS and MDR cases.

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PMCID: PMC10783999
PMID: 38223080

Conflict of interest statement: Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-23-694/coif). Y.X.J.W. serves as the Editor-in-Chief of Quantitative Imaging in Medicine and Surgery. The other authors have no conflicts of interest to declare.

18. Insights into the in-vitro Susceptibility and Drug-Drug Interaction Profiles Against Drug-Resistant and Susceptible Mycobacterium tuberculosis Clinical Isolates in Amhara, Ethiopia.

Infect Drug Resist. 2024 Jan 10;17:89-107. doi: 10.2147/IDR.S440947. eCollection 2024.

Seid A(1)(2), Girma Y(3), Dereb E(3), Kassa M(3), Nureddin S(4), Abebe A(3), Berhane N(2).

BACKGROUND: In Ethiopia, tuberculosis (TB) is a major public health problem. The aim of the study was to determine the in vitro susceptibility level of drugs and drug interaction profiles against drug-resistant and susceptible M. tuberculosis clinical isolates. A laboratory-based cross-sectional study was conducted between January 2023 and August 2023. GenoType MTBDRplus v.2.0 was facilitated in genetic mutation detection. Minimum inhibitory concentration (MIC) was determined using resazurin microtitre assay (REMA), while fractional inhibitory concentration index (FICI) using resazurin drug combination microtitre assay (REDCA) for in vitro quantitative susceptibility and drug interaction prediction.
RESULTS: Among 32 clinical isolates, a total of 14 (43.8%) RIF, 20 (62.5%) INH, 2 (6.3%) EMB-related resistant and 14 (43.8%) MDR isolates were identified. Five

of RIF-resistant isolates (55.6%) carrying rpoB common mutations at codon S450L were associated with high levels of RIF-resistance with MICs of ≥ 2µg/mL, whereas 100% of isolates harboring rpoB substitutions at codons D435V and H445Y were linked with moderate or low-level RIF-resistance in the MIC ranges from 0.5 to 1µg/mL. A proportion of 81.8% of isolates harboring katG S315T mutations were associated with high-level INH resistance (MIC ≥ 1µg/mL), while the 18.2% of isolates with S315T katG mutations and 100% of isolates with inhA C-15T mutations were linked to the low-level of INH resistance with MIC variability from 0.25 to 0.5µg/mL. Our results indicated that most FICIs of the dual drugs INH+RIF and INH+LEV combination for 9 (28.1%) and 4 (12.5%) INH-resistant isolates, respectively, were ≤0.5, whereas triple drugs INH+RIF+EMB, INH+RIF+LEV and INH+EMB+LEV combination for 6 (18.8%), 11 (34.4%) and 8 (25%) INH-resistant isolates were from 0.62 to 0.75, all showed synergistic effect.
CONCLUSION: The study highlights that isolates with rpoB S450L and katG S315T substitutions were associated with high level of RIF and INH resistance. It is concluded that REDCA can quantitatively determine anti-mycobacterial synergy and that LEV being of potential use against INH-resistant isolates including MDR-TB when combined with RIF+INH and INH+EMB.

DOI: 10.2147/IDR.S440947
PMCID: PMC10788062
PMID: 38223563

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

19. Impacts of body weight change on treatment outcomes in patients with multidrug-resistant tuberculosis in Northwest Ethiopia.

Sci Rep. 2024 Jan 4;14(1):508. doi: 10.1038/s41598-023-51026-y.

Wagnew F(1)(2)(3), Alene KA(4)(5), Kelly M(6), Gray D(7).

Measuring body weight during therapy has received insufficient attention in poor resource settings like Ethiopia. We aimed to investigate the association between weight change during therapy and treatment outcomes among patients with multidrug-resistant tuberculosis (MDR-TB) in northwest Ethiopia. This retrospective cohort study analysed data from patients with MDR-TB admitted between May 2015 to February 2022 at four treatment facilities in Northwest Ethiopia. We used the joint model (JM) to determine the association between weight change during therapy and treatment outcomes for patients with MDR-TB. A

total of 419 patients with MDR-TB were included in the analysis. Of these, 265 (63.3%) were male, and 255 (60.9%) were undernourished. Weight increase over time was associated with a decrease in unsuccessful treatment outcomes (adjusted hazard ratio (AHR): 0.96, 95% CI: 0.94 to 0.98). In addition, patients with undernutrition (AHR: 1.72, 95% CI: 1.10 to 2.97), HIV (AHR:1.79, 95% CI: 1.04 to 3.06), and clinical complications such as pneumothorax (AHR: 1.66, 95% CI: 1.03 to 2.67) were associated with unsuccessful treatment outcomes. The JM showed a significant inverse association between weight gain and unsuccessful MDR-TB treatment outcomes. Therefore, weight gain may be used as a surrogate marker for good TB treatment response in Ethiopia.

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PMCID: PMC10767082
PMID: 38177234 [Indexed for MEDLINE]

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

20. Preventive treatment for latent tuberculosis from Indian perspective.

Lung India. 2024 Jan 1;41(1):47-54. doi: 10.4103/lungindia.lungindia_336_23. Epub 2024 Jan 1.

Hashim Z(1), Tyagi R(1), Singh GV(2), Nath A(1), Kant S(3).

The persistent morbidity and mortality associated with tuberculosis (TB), despite our continued efforts, has been long recognized, and the rise in the incidence of drug-resistant TB adds to the preexisting concern. The bulk of the TB burden is confined to low-income countries, and rigorous efforts are made to detect, notify, and systematically treat TB. Efforts have been infused with renewed vigor and determination by the World Health Organization (WHO) to eliminate tuberculosis in the near future. Different health agencies worldwide are harvesting all possible strategies apart from consolidating ongoing practices, including prevention of the development of active disease by treating latent TB infection (LTBI). The guidelines for the same were already provided by the WHO and were then adapted in the Indian guidelines for the treatment of LTBI in 2021. While the long-term impact of TBI treatment is awaited, in this article, we aim to discuss the implications in the Indian context.

DOI: 10.4103/lungindia.lungindia_336_23

PMID: 38160459

21. Effect of delamanid on interim outcomes of bacteriological conversion amongst pediatric drug resistant tuberculosis cases in India.

Lung India. 2024 Jan 1;41(1):35-39. doi: 10.4103/lungindia.lungindia_72_23. Epub 2024 Jan 1.

Kalawadia D(1), Gandhi D(2), Dirkhipa TY(2), Jaiswal A(1), Shah D(3), Salve J(4), Parmar M(5), Sachdeva KS(6), Bodhanwala M(7), Shah I(8).

AIM: To determine the bacteriological conversion rate after 6 months of Delamanid (DLM) based treatment in children with drug-resistant tuberculosis (DR-TB) and determine factors associated with bacteriological conversion.
METHODS: This is a descriptive retrospective study done in children between the age of 6-17 years with DR-TB who received DLM-based therapy from October 2018 to May 2021. The drug resistance pattern of TB was detected using Xpert RIF/MTB and phenotypic drug sensitivity testing (DST) on TB-MGIT culture reports. Follow-up sputum TB MGIT culture was carried out monthly after DLM initiation for 6 months. Factors associated with sputum bacteriological conversion such as age, gender, pulmonary TB (PTB) versus disseminated TB, unilateral or bilateral lung involvement, type of DR-TB, prior treatment failure, and type of DR-TB regimen were analyzed.
RESULTS: Sixty patients received DLM of which two had extrapulmonary TB (EPTB) and sputum conversion could not be assessed. The mean age at presentation was 12.69 ± 3.03 years. Five patients (8.3%) died while on DLM treatment. On follow-up, 8 (13.7%) out of 58 patients had no sputum bacteriological conversion after 6 months of DLM initiation of which three patients were on salvage therapy; 46 (79.3%) had sputum bacteriological conversion within 6 months of DLM initiation.
CONCLUSION: Sputum bacteriological conversion rate was almost 80% at the end of 6 months of DLM-based treatment.

DOI: 10.4103/lungindia.lungindia_72_23
PMID: 38160457

22. Quabodepistat in combination with delamanid and bedaquiline in participants with drug-susceptible pulmonary tuberculosis: protocol for a multicenter, phase 2b/c, open-label, randomized, dose-finding trial to evaluate safety and efficacy.

Trials. 2024 Jan 19;25(1):70. doi: 10.1186/s13063-024-07912-5.

Dawson R(1), Diacon AH(2)(3), Takuva S(4)(5), Liu Y(6), Zheng B(6), Karwe V(6), Hafkin J(7).

BACKGROUND: Delamanid and bedaquiline are two of the most recently developed antituberculosis (TB) drugs that have been extensively studied in patients with multidrug-resistant TB. There is currently a need for more potent, less-toxic drugs with novel mechanisms of action that can be used in combination with these newer agents to shorten the duration of treatment as well as prevent the development of drug resistance. Quabodepistat (QBS) is a newly discovered inhibitor of decaprenylphosphoryl-β-D-ribose-2'-oxidase, an essential enzyme for Mycobacterium tuberculosis to synthesize key components of its cell wall. The objective of this study is to evaluate the safety, efficacy, and appropriate dosing of a 4-month regimen of QBS in combination with delamanid and bedaquiline in participants with drug-susceptible pulmonary TB in comparison with the 6-month standard treatment (i.e., rifampicin, isoniazid, ethambutol, and pyrazinamide).
METHODS: This phase 2b/c, open-label, randomized, parallel group, dose-finding trial will enroll approximately 120 participants (including no more than 15% with human immunodeficiency virus [HIV] coinfection) aged ≥ 18 to ≤ 65 years at screening with newly diagnosed pulmonary drug-sensitive TB from ~8 sites in South Africa. Following a screening period of up to 14 days, eligible participants will be randomized in a ratio of 1:2:2:1 to one of four arms. Randomization will be stratified by HIV status and the presence of bilateral cavitation on a screening chest x-ray. After the end of the treatment period, participants will be followed until 12 months post randomization. The primary efficacy endpoint is the proportion of participants achieving sputum culture conversion in Mycobacteria Growth Indicator Tube by the end of the treatment period. The safety endpoints consist of adverse events, clinical laboratory tests, vital signs, physical examination findings, and electrocardiographic changes.
DISCUSSION: QBS's potent bactericidal activity and distinct mechanism of action (compared with other TB drugs currently available for human use) may make it an ideal candidate for inclusion in a novel treatment regimen to improve efficacy and potentially prevent resistance to concomitant TB drugs. This trial will assess the effectiveness, safety, and dosing of a new, shorter, QBS-based, combination anti-TB treatment regimen.
TRIAL STATUS: ClinicalTrials.gov NCT05221502. Registered on February 3, 2022.

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PMCID: PMC10799444

PMID: 38243296 [Indexed for MEDLINE]

Conflict of interest statement: R. D. is an investigator for the study described in this paper, and they and/or their institutions will receive funding support from Otsuka Pharmaceutical Development & Commercialization, Inc. to conduct this study. A. H. D. is an investigator for the study described in this paper, and their institution will receive funding support from Otsuka Pharmaceutical Development & Commercialization, Inc. to conduct this study. S. T., Y. L., B. Z., V. K., and J. H. are employees of Otsuka Pharmaceutical Development & Commercialization, Inc.

23. Linezolid does not improve bactericidal activity of rifampin-containing first-line regimens in animal models of TB meningitis.

Int J Antimicrob Agents. 2024 Jan;63(1):107048. doi: 10.1016/j.ijantimicag.2023.107048. Epub 2023 Dec 5.

Tucker EW(1), Ruiz-Bedoya CA(2), Mota F(2), Erice C(1), Kim J(1), de Jesus P(2), Jahdav R(3), Bahr M(2), Flavahan K(2), Chen X(2), Peloquin CA(4), Freundlich JS(3), Jain SK(5).

Tuberculous meningitis (TB meningitis) is the most devastating form of tuberculosis (TB) and there is a critical need to optimize treatment. Linezolid is approved for multidrug resistant TB and has shown encouraging results in retrospective TB meningitis studies, with several clinical trials underway assessing its additive effects on high-dose (35 mg/kg/day) or standard-dose (10 mg/kg/day) rifampin-containing regimens. However, the efficacy of adjunctive linezolid to rifampin-containing first-line TB meningitis regimens and the tissue pharmacokinetics (PK) in the central nervous system (CNS) are not known. We therefore conducted cross-species studies in two mammalian (rabbits and mice) models of TB meningitis to test the efficacy of linezolid when added to the first-line TB regimen and measure detailed tissue PK (multicompartmental positron emission tomography [PET] imaging and mass spectrometry). Addition of linezolid did not improve the bactericidal activity of the high-dose rifampin-containing regimen in either animal model. Moreover, the addition of linezolid to standard-dose rifampin in mice also did not improve its efficacy. Linezolid penetration (tissue/plasma) into the CNS was compartmentalized with lower than previously reported brain and cerebrospinal fluid (CSF) penetration, which decreased further two weeks after initiation of treatment. These results provide important data regarding the addition of linezolid for the treatment of TB meningitis.

DOI: 10.1016/j.ijantimicag.2023.107048
PMID: 38061419 [Indexed for MEDLINE]

24. Treatment outcomes of retreated patients with isoniazid/rifampicin resistant pulmonary tuberculosis.

BMC Infect Dis. 2024 Jan 2;24(1):7. doi: 10.1186/s12879-023-08909-2.

Zhang L(#)(1), Han X(#)(2), Ge Q(2), Shu W(1), Sun Y(1), Gao J(1), Xie S(2), Wang J(3), Gao W(4).

BACKGROUND: About 8% of TB cases worldwide are estimated to have rifampicin-susceptible, isoniazid-resistant tuberculosis (Hr-TB), ranging from 5 to 11% regions. However, Hr-TB has not received much attention while comparing to be given high priority to the management of rifampicin-resistant tuberculosis (RR-TB). This study aimed to compare the differences of treatment effects for Hr-TB and RR-TB, so as to intensify the treatment and management of Hr-TB.
METHODS: A retrospective study was used to collect bacteriologically positive retreated patients with isoniazid/rifampicin resistant pulmonary tuberculosis, who were conducted at 29 tuberculosis control institutions in China from July 2009 to June 2021. We assessed effectiveness and safety of retreated patients with isoniazid/ rifampicin resistant pulmonary tuberculosis.
RESULTS: A total of 147 with either positive smear or cultures were enrolled, and 80 cases were in Hr-TB group and 67 cases were in RR-TB group. There was no significant difference in terms of age, sex, body mass, type of retreatment and comorbid diabetes between the two groups ($P > 0.05$). The rate of number of lesions involving lung fields ≥ 3 in Hr-TB group 75.9% (60/79) was significantly higher than RR-TB group 56.7% (38/67) ($\chi 2 = 6.077$, $P = 0.014$). There was no statistically significant difference ($P = 0.166$) with regard to the treatment outcomes of the two groups, the cure rates were 54.7% (41/75) and 53.6% (30/56), respectively, and the failure rate in Hr-TB group 22.7% (17/75) was 10% higher than RR-TB group 10.7% (6/56). The rate of negative sputum smear at the end of the second month (65.7%) in the Hr-TB group was significantly lower than that in the RR-TB group (85.7%) ($P = 0.025$). There were no significant differences in the incidences of serious adverse reactions and chest X-ray changes between the two groups ($P > 0.05$). During the 5-year follow-up, recurrence in the Hr-TB group (7 cases, 14.9%) was no significantly lower than that in the RR-TB group (4 cases, 11.8%) ($P = 0.754$).
CONCLUSION: The treatment of retreated Hr-TB patients was difficult and could be statistically similar or considerably worse than RR-TB. It's urgent to conduct further evaluation of the treatment status quo to guide the guideline development and clinical practice of Hr-TB patients.

DOI: 10.1186/s12879-023-08909-2
PMCID: PMC10759463
PMID: 38166793 [Indexed for MEDLINE]

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

25. Isoniazid Monoresistance and Antituberculosis Treatment Outcome in Persons With Pulmonary Tuberculosis in Brazil.

Open Forum Infect Dis. 2024 Jan 8;11(1):ofad691. doi: 10.1093/ofid/ofad691. eCollection 2024 Jan.

Araújo-Pereira M(1)(2)(3)(4), Arriaga MB(5), Carvalho ACC(6)(7), Spener-Gomes R(8)(9)(10), Schmaltz CAS(11), Nogueira BMF(2)(3)(4), Figueiredo MC(5), Turner MM(5), Cordeiro-Santos M(8)(9)(12), Rolla VC(11), Sterling TR(5), Andrade BB(1)(2)(3)(4), Kritski AL(6); Regional Prospective Observational Research for Tuberculosis (RePORT)-Brazil Consortium.

Collaborators: Rocha MS, Nascimento V, Santos SRN, Costa AG, Garcia LS, de Sousa Carvalho BK, de Loiola BP, Gomes-Silva A, Ignácio FP, Lourenço MC, Silva EC, Mello M, Souza AB, Benjamin A, Moreira ASR, de Oliveira JG, Cavalcante S, Durovni B, Lapa-E-Silva JR.

BACKGROUND: The high burden of drug-resistant tuberculosis (TB) is a problem to achieve the goals of the End TB Strategy by 2035. Whether isoniazid monoresistance (Hr) affects anti-TB treatment (ATT) outcomes remains unknown in high-burden countries.
METHODS: We evaluated determinants of ATT outcome among pulmonary TB cases reported to the National Notifiable Disease Information System (SINAN) between June 2015 and June 2019, according to drug sensitivity testing (DST) results. Binomial logistic regression models were employed to evaluate whether Hr was associated with an unfavorable ATT outcome: death or failure, compared to cure or treatment completion.
RESULTS: Among 60 804 TB cases reported in SINAN, 21 197 (34.9%) were included in the study. In this database, the frequency of unfavorable outcomes was significantly higher in those with Hr in contrast to isoniazid-sensitive persons with pulmonary TB (9.1% vs 3.05%; P < .001). Using a binomial logistic regression model, Hr was independently associated with unfavorable outcomes (odds ratio, 3.34 [95% confidence interval, 2.06-5.40]; P < .001).

CONCLUSIONS: Hr detected prior to ATT was predictive of unfavorable outcomes at the national level in Brazil. Our data reinforce the need for high-TB-burden countries to prioritize DST to detect Hr. Effective treatment regimens for Hr-TB are needed to improve outcomes.

DOI: 10.1093/ofid/ofad691
PMCID: PMC10785213
PMID: 38221983

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

26. Role of the first WHO mutation catalogue in the diagnosis of antibiotic resistance in Mycobacterium tuberculosis in the Valencia Region, Spain: a retrospective genomic analysis.

Lancet Microbe. 2024 Jan;5(1):e43-e51. doi: 10.1016/S2666-5247(23)00252-5. Epub 2023 Dec 4.

García-Marín AM(1), Cancino-Muñoz I(1), Torres-Puente M(2), Villamayor LM(3), Borrás R(4), Borrás-Máñez M(5), Bosque M(6), Camarena JJ(7), Colomer-Roig E(8), Colomina J(4), Escribano I(9), Esparcia-Rodríguez O(10), Gil-Brusola A(11), Gimeno C(12), Gimeno-Gascón A(13), Gomila-Sard B(14), González-Granda D(15), Gonzalo-Jiménez N(16), Guna-Serrano MR(12), López-Hontangas JL(11), Martín-González C(17), Moreno-Muñoz R(14), Navarro D(4), Navarro M(18), Orta N(19), Pérez E(20), Prat J(21), Rodríguez JC(13), Ruiz-García MM(16), Vanaclocha H(20); Valencia Region Tuberculosis Working Group; González-Candelas F(22), Furió V(23), Comas I(24).

BACKGROUND: In June, 2021, WHO published the most complete catalogue to date of resistance-conferring mutations in Mycobacterium tuberculosis. Here, we aimed to assess the performance of genome-based antimicrobial resistance prediction using the catalogue and its potential for improving diagnostics in a real low-burden setting.
METHODS: In this retrospective population-based genomic study M tuberculosis isolates were collected from 25 clinical laboratories in the low-burden setting of the Valencia Region, Spain. Culture-positive tuberculosis cases reported by regional public health authorities between Jan 1, 2014, and Dec 31, 2016, were included. The drug resistance profiles of these isolates were predicted by the genomic identification, via whole-genome sequencing (WGS), of the

high-confidence resistance-causing variants included in the catalogue and compared with the phenotype. We determined the minimum inhibitory concentration (MIC) of the isolates with discordant resistance profiles using the resazurin microtitre assay.
FINDINGS: WGS was performed on 785 M tuberculosis complex culture-positive isolates, and the WGS resistance prediction sensitivities were: 85·4% (95% CI 70·8-94·4) for isoniazid, 73·3% (44·9-92·2) for rifampicin, 50·0% (21·1-78·9) for ethambutol, and 57·1% (34·0-78·2) for pyrazinamide; all specificities were more than 99·6%. Sensitivity values were lower than previously reported, but the overall pan-susceptibility accuracy was 96·4%. Genotypic analysis revealed that four phenotypically susceptible isolates carried mutations (rpoB Leu430Pro and rpoB Ile491Phe for rifampicin and fabG1 Leu203Leu for isoniazid) known to give borderline resistance in standard phenotypic tests. Additionally, we identified three putative resistance-associated mutations (inhA Ser94Ala, katG Leu48Pro, and katG Gly273Arg for isoniazid) in samples with substantially higher MICs than those of susceptible isolates. Combining both genomic and phenotypic data, in accordance with the WHO diagnostic guidelines, we could detect two new multidrug-resistant cases. Additionally, we detected 11 (1·6%) of 706 isolates to be monoresistant to fluoroquinolone, which had been previously undetected.
INTERPRETATION: We showed that the WHO catalogue enables the detection of resistant cases missed in phenotypic testing in a low-burden region, thus allowing for better patient-tailored treatment. We also identified mutations not included in the catalogue, relevant at the local level. Evidence from this study, together with future updates of the catalogue, will probably lead in the future to the partial replacement of culture testing with WGS-based drug susceptibility testing in our setting.
FUNDING: European Research Council and the Spanish Ministerio de Ciencia.

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PMCID: PMC10790317
PMID: 38061383 [Indexed for MEDLINE]

Conflict of interest statement: Declaration of interests IC received consultancy fees from the Foundation for Innovative New Diagnostics. IC and VF have participated in the elaboration of the WHO catalogue used in this study. All other authors declare no competing interests.

27. Phenotype versus genotype discordant rifampicin susceptibility testing in tuberculosis: implications for a diagnostic accuracy.

Microbiol Spectr. 2024 Jan 11;12(1):e0163123. doi: 10.1128/spectrum.01631-23. Epub 2023 Nov 20.

Qadir M(1)(2), Faryal R(2), Khan MT(3)(4), Khan SA(1), Zhang S(5), Li W(6), Wei DQ(3)(7)(8), Tahseen S(1), McHugh TD(9).

An accurate diagnosis of drug resistance in clinical isolates is an important step for better treatment outcomes. The current study observed a higher discordance rate of rifampicin resistance on Mycobacteria Growth Indicator Tube (MGIT) drug susceptibility testing (DST) than Lowenstein-Jenson (LJ) DST when compared with the rpoB sequencing. We detected a few novel mutations and their combination in rifampicin resistance isolates that were missed by MGIT DST and may be useful for the better management of tuberculosis (TB) treatment outcomes. Few novel deletions in clinical isolates necessitate the importance of rpoB sequencing in large data sets in geographic-specific locations, especially high-burden countries. We explored the discordance rate on MGIT and LJ, which is important for the clinical management of rifampicin resistance to avoid the mistreatment of drug-resistant TB. Furthermore, MGIT-sensitive isolates may be subjected to molecular methods of diagnosis for further confirmation and treatment options.

DOI: 10.1128/spectrum.01631-23
PMCID: PMC10783056
PMID: 37982632 [Indexed for MEDLINE]

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

28. Quantitative measurement of antibiotic resistance in Mycobacterium tuberculosis reveals genetic determinants of resistance and susceptibility in a target gene approach.

Nat Commun. 2024 Jan 12;15(1):488. doi: 10.1038/s41467-023-44325-5.

CRyPTIC Consortium.

Collaborators: Barilar I, Battaglia S, Borroni E, Brandao AP, Brankin A, Cabibbe AM, Carter J, Chetty D, Cirillo DM, Claxton P, Clifton DA, Cohen T, Coronel J, Crook DW, Dreyer V, Earle SG, Escuyer V, Ferrazoli L, Fowler PW, Gao GF, Gardy J, Gharbia S, Ghisi KT, Ghodousi A, Gibertoni Cruz AL, Grandjean L, Grazian C, Groenheit R, Guthrie JL, He W, Hoffmann H, Hoosdally SJ, Hunt M, Iqbal Z, Ismail NA, Jarrett L, Joseph L, Jou R, Kambli P, Khot R, Knaggs J, Koch A, Kohlerschmidt D, Kouchaki S, Lachapelle AS, Lalvani A, Lapierre SG, Laurenson IF, Letcher B, Lin WH, Liu C, Liu D, Malone KM, Mandal A, Mansjö M, Calisto

Matias DVL, Meintjes G, de Freitas Mendes F, Merker M, Mihalic M, Millard J, Miotto P, Mistry N, Moore D, Musser KA, Ngcamu D, Nhung HN, Niemann S, Nilgiriwala KS, Nimmo C, O'Donnell M, Okozi N, Oliveira RS, Omar SV, Paton N, Peto TEA, Pinhata JMW, Plesnik S, Puyen ZM, Rabodoarivelo MS, Rakotosamimanana N, Rancoita PMV, Rathod P, Robinson ER, Rodger G, Rodrigues C, Rodwell TC, Roohi A, Santos-Lazaro D, Shah S, Smith G, Kohl TA, Solano W, Spitaleri A, Steyn AJC, Supply P, Surve U, Tahseen S, Thuong NTT, Thwaites G, Todt K, Trovato A, Utpatel C, Van Rie A, Vijay S, Walker AS, Walker TM, Warren R, Werngren J, Wijkander M, Wilkinson RJ, Wilson DJ, Wintringer P, Xiao YX, Yang Y, Yanlin Z, Yao SY, Zhu B.

Update of
Res Sq. 2023 Oct 02;:

The World Health Organization has a goal of universal drug susceptibility testing for patients with tuberculosis. However, molecular diagnostics to date have focused largely on first-line drugs and predicting susceptibilities in a binary manner (classifying strains as either susceptible or resistant). Here, we used a multivariable linear mixed model alongside whole genome sequencing and a quantitative microtiter plate assay to relate genomic mutations to minimum inhibitory concentration (MIC) in 15,211 Mycobacterium tuberculosis clinical isolates from 23 countries across five continents. We identified 492 unique MIC-elevating variants across 13 drugs, as well as 91 mutations likely linked to hypersensitivity. Our results advance genetics-based diagnostics for tuberculosis and serve as a curated training/testing dataset for development of drug resistance prediction algorithms.

DOI: 10.1038/s41467-023-44325-5
PMCID: PMC10786857
PMID: 38216576 [Indexed for MEDLINE]

Conflict of interest statement: E.R. is employed by Public Health England and holds an honorary contract with Imperial College London. I.F.L. is Director of the Scottish Mycobacteria Reference Laboratory. S.N. receives funding from German Center for Infection Research, Excellenz Cluster Precision Medicine in Chronic Inflammation, Leibniz Science Campus Evolutionary Medicine of the LUNG (EvoLUNG)tion EXC 2167. P.S. is a consultant at Genoscreen. T.R. is funded by NIH and DoD and receives salary support from the non-profit organization FIND. T.R. is a co-founder, board member and shareholder of Verus Diagnostics Inc, a company that was founded with the intent of developing diagnostic assays. Verus Diagnostics was not involved in any way with data collection, analysis or publication of the results. T.R. has not received any financial support from Verus Diagnostics. UCSD Conflict of Interest office has reviewed and approved

T.R.'s role in Verus Diagnostics Inc. T.R. is a co-inventor of a provisional patent for a TB diagnostic assay (provisional patent #: 63/048.989). T.R. is a co-inventor on a patent associated with the processing of TB sequencing data (European Patent Application No. 14840432.0 and USSN 14/912,918). T.R. has agreed to "donate all present and future interest in and rights to royalties from this patent" to UCSD to ensure that he does not receive any financial benefits from this patent. S.S. is working and holding ESOPs at HaystackAnalytics Pvt. Ltd. (Product: Using whole genome sequencing for drug susceptibility testing for Mycobacterium tuberculosis). The remaining authors declare no competing interest.

29. Mistaken identity: Reporting two cases of rare forms of extrapulmonary tuberculosis in Solomon Islands.

Int J Surg Case Rep. 2024 Jan;114:109141. doi: 10.1016/j.ijscr.2023.109141. Epub 2023 Dec 10.

Bush D(1), Fiuramo F(2), Liligeto J(2), Ipulu L(2), Diau J(2), Jagilly R(2).

INTRODUCTION AND IMPORTANCE: Extrapulmonary tuberculosis (EPTB) is a relatively rare and difficult-to-diagnose manifestation of Myobacterium tuberculosis (TB) infection.
CASE PRESENTATION: This study reports the cases of a 47-year-old male and a 35-year old female with rare forms of EPTB who sought medical care in Solomon Islands. Both patients presented with nondescript symptoms and a chief complaint of pain. Initial diagnosis for the male and female patient was an abacterial colon polypoid mass and a urinary tract infection (UTI) respectively. Following unsuccessful treatment for UTI and further investigation, the surgical team diagnosed the female patient with a tuberculosis spondylitis and a bilateral psoas abscess. The male patient was subsequently diagnosed with isolated colonic tuberculosis. After starting medication, the patients were discharged and prescribed 9-month treatment regimens. During outpatient treatment both patients reported suboptimal adherence. The female patient resumed treatment and showed improvement while the male patient discontinued treatment, experienced worsening symptoms, and ultimately died.
CLINICAL DISCUSSION: The nonspecific symptoms of extrapulmonary TB infection make it difficult to diagnose. Cases of rare forms of EPTB are particularly challenging to identify. Misdiagnosis may further increase the likelihood of mortality and morbidity in these cases. Intensive medication counseling, patient outreach, and regularly scheduled follow-up visits may reduce the incidence of poor adherence and reduce the risk of developing drug-resistant TB.
CONCLUSION: Medical practitioners in tuberculosis-endemic countries like Solomon Islands should maintain a high clinical index of suspicion in diagnosing EPTB.

Future research should investigate the prevalence of TB and EPTB in the Solomon Islands.

DOI: 10.1016/j.ijscr.2023.109141
PMCID: PMC10726230
PMID: 38086130

Conflict of interest statement: Declaration of competing interest The authors report no declaration of competing interest.

30. Acquiring of photosensitivity by Mycobacterium tuberculosis in vitro and inside infected macrophages is associated with accumulation of endogenous Zn-porphyrins.

Sci Rep. 2024 Jan 8;14(1):846. doi: 10.1038/s41598-024-51227-z.

Shleeva MO(1), Linge IA(2), Gligonov IA(3), Vostroknutova GN(3), Shashin DM(3), Tsedilin AM(3), Apt AS(2), Kaprelyants AS(3), Savitsky AP(4).

Mycobacterium tuberculosis (Mtb) is able to transition into a dormant state, causing the latent state of tuberculosis. Dormant mycobacteria acquire resistance to all known antibacterial drugs and can survive in the human body for decades before becoming active. In the dormant forms of M. tuberculosis, the synthesis of porphyrins and its Zn-complexes significantly increased when 5-aminolevulinic acid (ALA) was added to the growth medium. Transcriptome analysis revealed an activation of 8 genes involved in the metabolism of tetrapyrroles during the Mtb transition into a dormant state, which may lead to the observed accumulation of free porphyrins. Dormant Mtb viability was reduced by more than 99.99% under illumination for 30 min (300 J/cm2) with 565 nm light that correspond for Zn-porphyrin and coproporphyrin absorptions. We did not observe any PDI effect in vitro using active bacteria grown without ALA. However, after accumulation of active cells in lung macrophages and their persistence within macrophages for several days in the presence of ALA, a significant sensitivity of active Mtb cells (ca. 99.99%) to light exposure was developed. These findings create a perspective for the treatment of latent and multidrug-resistant tuberculosis by the eradication of the pathogen in order to prevent recurrence of this disease.

DOI: 10.1038/s41598-024-51227-z

PMCID: PMC10774309
PMID: 38191600 [Indexed for MEDLINE]

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

31. Loss-of-function mutations in ndh do not confer delamanid, ethionamide, isoniazid, or pretomanid resistance in Mycobacterium tuberculosis.

Antimicrob Agents Chemother. 2024 Jan 10;68(1):e0109623. doi: 10.1128/aac.01096-23. Epub 2023 Dec 1.

Pandey S(#)(1), Vilchèze C(#)(2), Werngren J(#)(3), Bainomugisa A(1), Mansjö M(3), Groenheit R(3), Miotto P(4), Cirillo DM(4), Coulter C(1), Baulard AR(5), Schön T(6)(7)(8), Jacobs WR Jr(2), Djaout K(#)(5), Köser CU(#)(9).

Results from clinical strains and knockouts of the H37Rv and CDC1551 laboratory strains demonstrated that ndh (Rv1854c) is not a resistance-conferring gene for isoniazid, ethionamide, delamanid, or pretomanid in Mycobacterium tuberculosis. This difference in the susceptibility to NAD-adduct-forming drugs compared with other mycobacteria may be driven by differences in the absolute intrabacterial NADH concentration.

DOI: 10.1128/aac.01096-23
PMCID: PMC10777854
PMID: 38038476 [Indexed for MEDLINE]

Conflict of interest statement: D.M.C. is the co-chair of the Working Group of the Stop TB Partnership New Diagnostics and is an unpaid member of EUCAST subcommittee for antimicrobial susceptibility testing of mycobacteria, the CLSI mycobacterial committee, and the WHO Strategic and Technical Advisory Group for diagnostics. C.U.K. is a consultant for Becton Dickinson, the Foundation for Innovative New Diagnostics, the TB Alliance, and the WHO Global TB Programme. C.U.K.'s consulting for Becton Dickinson involves a collaboration with Janssen and Thermo Fisher Scientific. C.U.K. is collaborating with PZA Innovation and is an unpaid advisor to Cepheid and GenoScreen. C.U.K. worked as a consultant for the Stop TB Partnership and the WHO Regional Office for Europe. C.U.K. gave a paid educational talk for Oxford Immunotec. C.U.K. was an unpaid advisor to BioVersys.

32. Management of rifampicin-resistant tuberculosis in conflict-affected areas: The case of Iraq.

PLoS One. 2024 Jan 19;19(1):e0296952. doi: 10.1371/journal.pone.0296952. eCollection 2024.

Tesfahun HM(1), Al-Salihi L(2), Abdulkareem Al-Ani N(2), Mankhi AA(2), Mohammed A(3), Lim CAE(3), Al-Hilfi RA(4), Jouego CG(5), Decroo T(6), Moussally K(7), Ferlazzo G(8), Isaakidis P(8)(9).

Since December 2019, the World Health Organization (WHO) has encouraged National Tuberculosis Programs to deprioritize the use of injectable-containing regimens and roll-out all-oral bedaquiline-containing regimens for rifampicin-resistant tuberculosis (RR-TB) treatment. Consequently, Iraq gradually replaced the injectable-containing regimen with an all-oral regimen, including bedaquiline. To assess treatment enrolment and outcomes of both regimens during a transitioning phase in Iraq, where health system services are recovering from decades of war, we conducted a nationwide retrospective cohort study using routinely collected programmatic data for patients enrolled between 2019-2021. We describe treatment enrolment and use logistic regression to identify predictors of unfavorable treatment outcomes (failure, death, or lost to follow-up), including regimen type. Nationwide, a total of 301 RR-TB patients started treatment, of whom 167 concluded treatment. The proportion of patients enrolled on the all-oral regimen increased from 53.2% (50/94) in 2020, to 75.5% (80/106) in 2021. Successful treatment was achieved in 82.1% (32/39) and 63.3% (81/128), for all-oral and injectable-containing regimens respectively. Moreover, the proportion of lost to follow-up was lower among those treated with the all-oral versus the long injectable-containing regimen; respectively 2.6% (1/39) versus 17.9% (23/128: p = 0.02). Unfavorable treatment outcome was associated with male gender (aOR 2.12, 95%CI:1.02-4.43) and age <15 years (vs 30-49 years, aOR 5.80, 95%CI:1.30-25.86). Regimen type (aOR 2.37, 95%CI: 0.91-6.13) was not significantly associated with having an unfavorable treatment outcome. In Iraq, the use of bedaquiline-containing all-oral regimen resulted in a high treatment success and reduced lost to follow-up.

DOI: 10.1371/journal.pone.0296952
PMCID: PMC10798474
PMID: 38241233 [Indexed for MEDLINE]

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

33. Development and validation of a liquid chromatography tandem mass spectrometry assay for the analysis of bedaquiline and M2 in breast milk.

J Mass Spectrom Adv Clin Lab. 2023 Dec 13;31:8-16. doi: 10.1016/j.jmsacl.2023.12.001. eCollection 2024 Jan.

Mkhize B(1), Court R(1), Castel S(1), Joubert A(1), van der Merwe M(1), Wiesner L(1).

OBJECTIVE: To develop and validate an assay for the analysis of bedaquiline and its M2 metabolite in human breast milk.
METHODS: The analytes were extracted using solid phase extraction following protein precipitation. Quantification was performed with liquid chromatography coupled with tandem mass spectrometry. Chromatographic separation was achieved using gradient chromatography on a Poroshell 120 SB-C18 analytical column at 40 °C, with a flow rate of 350 µL/minute and a total run time of eight minutes. An AB Sciex 3000 mass spectrometer with electrospray ionization in the positive mode was used for detection, employing multiple reaction monitoring scan mode. Bedaquiline-d6 and M2-d3-13C were used as internal standards.
RESULTS: Calibrations curves for bedaquiline and M2 exhibited quadratic (weighted 1/x concentration) regressions over the respective concentration ranges of 0.0780 to 5.00 µg/mL and 0.0312 to 2.00 µg/mL. Inter- and intra-day validation accuracies ranged between 96.7 % and 103.5 % for bedaquiline, and 104.2 % to 106.5 % for M2, with a coefficient of variation below 9.2 % for both compounds.
CONCLUSION: The developed assay demonstrated selectivity and robustness, enabling differentiation between bedaquiline and M2 within the context of endogenous compounds from six separate lots of breast milk samples. Successful application was observed in the analysis of breast milk samples sourced from patients treated for multidrug-resistant tuberculosis within a clinical study setting.

DOI: 10.1016/j.jmsacl.2023.12.001
PMCID: PMC10770620
PMID: 38188986

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

34. Sudapyridine (WX-081) antibacterial activity against Mycobacterium avium, Mycobacterium abscessus, and Mycobacterium chelonae in vitro and in vivo.

mSphere. 2024 Jan 19:e0051823. doi: 10.1128/msphere.00518-23. Online ahead of print.

Zheng L(#)(1), Wang H(#)(1), Qi X(1), Zhang W(1), Wang B(1), Fu L(1), Chen X(1), Chen X(2)(3), Lu Y(1).

Sudapyridine (WX-081) is a structural analog of bedaquiline (BDQ), which shows anti-tuberculosis and non-tuberculous mycobacteria (NTM) activities but, unlike BDQ, did not prolong QT interval in animal model studies. This study evaluated the antibacterial activity of this novel compound against Mycobacterium avium, Mycobacterium abscessus, and Mycobacterium chelonae in vitro and in vivo. The minimum inhibitory concentration (MIC) of WX-081 against three kinds of non-tuberculous mycobacteria (NTM) clinical strains was determined using microplate-based alamarBlue assay (MABA), and the antibacterial activity of WX-081 against NTM in J774A.1 cells and mice was evaluated. MIC ranges of WX-081 against clinical strains of M. avium and M. abscessus were 0.05-0.94 µg/mL, 0.88-7.22 µg/mL (M. abscessus subsp. abscessus), and 0.22-8.67 µg/mL (M. abscessus subsp. massiliense), respectively, which were slightly higher than those of BDQ. For M. avium, M. abscessus, and M. chelonae, WX-081 can reduce the intracellular bacterial load by 0.13-1.18, 0.18-1.50, and 0.17-1.03 log10 colony forming units (CFU)/mL, respectively, in a concentration-dependent manner. WX-081 has bactericidal activity against three NTM species in mice. WX-081 exhibited anti-NTM activity to the same extent as BDQ both in vivo and in vitro. WX-081 is a promising clinical candidate and should be studied further in clinical trials.IMPORTANCEDue to the rapidly increased cases globally, non-tuberculous mycobacteria (NTM) disease has become a significant public health problem. NTM accounted for 11.57% of all mycobacterial isolates in China, with a high detection rate of Mycobacterium abscessus, Mycobacterium avium, and Mycobacterium chelonae during 2000-2019. Treatment of NTM infection is often challenging, as natural resistance to most antibiotics is quite common among different NTM species. Hence, identifying highly active anti-NTM agents is a priority for potent regimen establishment. The pursuit of new drugs to treat multidrug-resistant tuberculosis may also identify some agents with strong activity against NTM. Sudapyridine (WX-081) is a structural analog of bedaquiline (BDQ), which was developed to retain the anti-tuberculosis efficacy but eliminates the severe side effects of BDQ. This study initially evaluated the antimicrobial activity of this novel compound against M. avium, M. abscessus, and M. chelonae in vitro, in macrophages and mice, respectively.

DOI: 10.1128/msphere.00518-23
PMID: 38240581

Pub Med Non-Open Access

35. [Treatment of MDR, pre-XDR, XDR and rifampicin resistant tuberculosis or in case of intolerance to at least rifampicin in Austria, Germany and Switzerland - Amendment dated 19.09.2023 to the Sk2-Guideline: Tuberculosis in adulthood of the German Central Committee against Tuberculosis (DZK) on behalf of the German Respiratory Society (DGP)].

Pneumologie. 2024 Jan;78(1):35-46. doi: 10.1055/a-2182-1609. Epub 2023 Nov 6.

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

Otto-Knapp R(1), Bauer T(1)(2), Brinkmann F(3), Feiterna-Sperling C(4), Friesen I(5), Geerdes-Fenge H(6), Hartmann P(7), Häcker B(1), Hauer B(8), Haas W(8), Heyckendorf J(9), Kuhns M(5), Lange C(10)(11)(12)(13), Maurer FP(14), Nienhaus A(15), Priwitzer M(16), Richter E(17), Salzer HJF(18)(19)(20), Schoch O(21), Schönfeld N(2), Schaberg T(1).

In December 2022, based on the assessment of new evidence, the World Health Organization (WHO) updated its guidelines for the treatment of drug-resistant tuberculosis (TB). The evaluation of both, these recommendations, and the latest study data, makes it necessary to update the existing guidelines on the treatment of at least rifampicin-resistant tuberculosis for the German-speaking region, hereby replacing the respective chapters. A shortened MDR-TB treatment of at least 6 month using the fixed and non-modifiable drug combination of bedaquiline, pretomanid, linezolid, and moxifloxacin (BPaLM) is now also recommended for Germany, Austria, and Switzerland under certain conditions. This recommendation applies to TB cases with proven rifampicin resistance, including rifampicin monoresistance. For treatment of pre-extensively drug resistant TB (pre-XDR-TB), an individualized treatment for 18 months adjusted to resistance data continues to be the primary recommendation. The non-modifiable drug combination of bedaquiline, pretomanid, and linezolid (BPaL) may be used alternatively in pre-XDR TB if all prerequisites are met. The necessary prerequisites for the use of BPaLM and BPaL are presented in this amendment to the S2k guideline for 'Tuberculosis in adulthood'.

DOI: 10.1055/a-2182-1609
PMID: 37931778 [Indexed for MEDLINE]

Conflict of interest statement: Informationen zu Interessenkonflikten finden Sie auf den Seiten der AWMF (http://www.awmf.org/leitlinien/awmf-regelwerk.html).

36. Transforming growth factor-β, Interleukin-23 and interleukin-1β modulate TH22 response during active multidrug-resistant tuberculosis.

Immunology. 2024 Jan;171(1):45-59. doi: 10.1111/imm.13698. Epub 2023 Sep 16.

Imperiale BR(1), Gamberale A(2), Yokobori N(3), García A(2), Bartoletti B(2), Aidar O(2), López B(3), Cruz V(2), González Montaner P(2)(4), Palmero DJ(2)(4), de la Barrera S(1).

We previously reported that patients with multidrug-resistant tuberculosis (MDR-TB) showed low systemic and Mtb-induced Th22 responses associated to high sputum bacillary load and severe lung lesions suggesting that Th22 response could influence the ability of these patients to control bacillary growth and tissue damage. In MDR-TB patients, the percentage of IL-22+ cells inversely correlates with the proportion of senescent PD-1+ T cells. Herein, we aimed to evaluate the pathways involved on the regulation of systemic and Mtb-induced Th22 response in MDR-TB and fully drug-susceptible TB patients (S-TB) and healthy donors. Our results show that while IL-1β and IL-23 promote Mtb-induced IL-22 secretion and expansion of IL-22+ cells, TGF-β inhibits this response. Systemic and in vitro Mtb-induced Th22 response inversely correlates with TGF-β amounts in plasma and in PBMC cultures respectively. The number of circulating PD-1+ T cells directly correlates with plasmatic TGF-β levels and blockade of PD-1/PD-L1 signalling enhances in vitro Mtb-induced expansion of IL-22+ cells. Thus, TGF-β could also inhibit Th22 response through upregulation of PD-1 expression in T cells. Higher percentage of IL-23+ monocytes was observed in TB patients. In contrast, the proportion of IL-1β+ monocytes was lower in TB patients with bilateral lung cavities (BCC) compared to those patients with unilateral cavities (UCC). Interestingly, TB patients with BCC showed higher plasmatic and Mtb-induced TGF-β secretion than patients with UCC. Thus, high TGF-β secretion and subtle differences in IL-23 and IL-1β expression could diminish systemic and in vitro Mtb-induced Th22 response along disease progression in TB patients.

DOI: 10.1111/imm.13698
PMID: 37715690 [Indexed for MEDLINE]

37. Clinical research progress of novel antituberculosis drugs on multidrug-resistant tuberculosis.

Postgrad Med J. 2024 Jan 10:qgad140. doi: 10.1093/postmj/qgad140. Online ahead of print.

Zhong X(1), Lin A(2), Luo J(1), Li Y(1), Chen J(1), Ning C(1), Cao F(1).

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(2)Department of Cardiothoracic Surgery, Red Cross Hospital of Yulin City, Yulin, Guangxi 537000, China.

Multidrug-resistant tuberculosis (MDR-TB) has become a critical challenge to public health, and the prevention and treatment of MDR-TB are of great significance in reducing the global burden of tuberculosis. How to improve the effectiveness and safety of chemotherapy for MDR-TB is a pressing issue that needs to be addressed in tuberculosis control efforts. This article provides a comprehensive review of the clinical application of new antituberculosis drugs in MDR-TB, aiming to provide a scientific basis for the prevention and treatment strategy of MDR-TB.

DOI: 10.1093/postmj/qgad140
PMID: 38200633

38. A descriptive study on isoniazid resistance-associated mutations, clustering and treatment outcomes of drug-resistant tuberculosis in a high burden country.

Eur J Clin Microbiol Infect Dis. 2024 Jan;43(1):73-85. doi: 10.1007/s10096-023-04693-8. Epub 2023 Nov 9.

Pinhata JMW(1), Ferrazoli L(2), Mendes FF(2), Gonçalves MG(2), Rabello MCDS(3), Ghisi KT(2), Simonsen V(2), Cavalin RF(4), Lindoso AABP(4), de Oliveira RS(2).

PURPOSE: To describe katG and inhA mutations, clinical characteristics, treatment outcomes and clustering of drug-resistant tuberculosis (TB) in the State of São Paulo, southeast Brazil.
METHODS: Mycobacterium tuberculosis isolates from patients diagnosed with drug-resistant TB were screened for mutations in katG and inhA genes by line probe assay and Sanger sequencing, and typed by IS6110-restriction fragment-length polymorphism for clustering assessment. Clinical, epidemiological and demographic data were obtained from surveillance information systems for TB.
RESULTS: Among the 298 isolates studied, 127 (42.6%) were isoniazid-monoresistant, 36 (12.1%) polydrug-resistant, 93 (31.2%) MDR, 16 (5.4%) pre-extensively drug-resistant (pre-XDR), 9 (3%) extensively drug-resistant (XDR) and 17 (5.7%) susceptible after isoniazid retesting. The

frequency of katG 315 mutations alone was higher in MDR isolates, while inhA promoter mutations alone were more common in isoniazid-monoresistant isolates. Twenty-six isolates phenotypically resistant to isoniazid had no mutations either in katG or inhA genes. The isolates with inhA mutations were found more frequently in clusters (75%) when compared to the isolates with katG 315 mutations (59.8%, p = 0.04). In our population, being 35-64 years old, presenting MDR-, pre-XDR- or XDR-TB and being a retreatment case were associated with unfavourable TB treatment outcomes.
CONCLUSION: We found that katG and inhA mutations were not equally distributed between isoniazid-monoresistant and MDR isolates. In our population, clustering was higher for isolates with inhA mutations. Finally, unfavourable TB outcomes were associated with specific factors.

DOI: 10.1007/s10096-023-04693-8
PMID: 37943394 [Indexed for MEDLINE]

39. Novel and Innovative Approach of Nanotechnology with their Applications in the Management of Infectious Disease, Tuberculosis: An Overview.

Recent Pat Nanotechnol. 2024;18(2):140-163. doi: 10.2174/1872210516666220523122724.

Singh S(1), Ahuja A(2).

Tuberculosis (TB) is considered a significant health problem caused by Mycobacterium tuberculosis. It is one of the second-deadly infectious diseases right after AIDS. Several factors such as poor patient compliance, high dose intake, low drug bioavailability and prolonged treatment of disease are responsible for the prevalence of multi-drug resistance tuberculosis and extensively drug-resistant tuberculosis cases. Therefore, developing such drug-resistant bacterial strains has created a robust and efficient system that can improve the therapeutic effectiveness of anti-tubercular drugs. This review manuscript highlights the therapeutic outcomes of a nanotechnology-based drug delivery system in treating TB. Various novel nanoformulations for anti-mycobacterial drugs have been explored. Such novel approaches would have shown several advantages such as sustained/controlled drug release, reduced dose frequency, and resolved poor patient compliance over many free anti-tubercular drugs. This framework will provide valuable information on various nanoparticle-based technology employed in treating TB infectious disease. Patent data were searched in google patent and nanoformulations outcomes for TB management improves health of patients.

DOI: 10.2174/1872210516666220523122724
PMID: 35616678 [Indexed for MEDLINE]

40. Effect of Bedaquiline and Delamanid Pharmacokinetics on Sputum Culture Conversion and Adverse Events in Drug-Resistant Tuberculosis.

Ther Drug Monit. 2024 Jan 1. doi: 10.1097/FTD.0000000000001164. Online ahead of print.

Bhatnagar AK(1), Hemanthkumar AK(2), Muthu Vijayalakshmi M(2), Vohra V(3), Padmapriyadarsini C(2), Ramesh PM(4), Taneja G(1), Chavan VN(5), Jeyadeepa B(2), Bhui NK(5), Solanki R(6).

BACKGROUND: Pharmacokinetic studies of bedaquiline and delamanid in patients with pre-extensively drug-resistant tuberculosis (pre-XDR TB) will help in the optimization of these drugs for both culture conversion and adverse events.
METHODS: A prospective cohort of 165 adult patients (56% male with mean [SD] age 29 [9.7] years) with pre-XDR TB was treated with bedaquiline, delamanid, clofazimine, and linezolid for 24 weeks at 5 sites in India. Bedaquiline was administered at 400 mg daily for 2 weeks followed by 200 mg thrice weekly for 22 weeks, whereas delamanid was administered at 100 mg twice daily. In 23 consenting participants at 8 and 16 weeks of treatment, blood was collected at 0, 2, 4, 5, 6, 8, 12, and 24 hours postdosing for an intense pharmacokinetic study. Pharmacokinetic parameters were correlated with sputum culture conversion and adverse events.
RESULTS: The mean (SD) age and weight of patients were 30 (10) years and 54 kg, respectively. The median minimum concentration (Cmin) and time-concentration curve (AUC) for bedaquiline, respectively, were 0.6 mcg/mL and 27 mcg/mL·h at week 8 and 0.8 mcg/mL and 36 mcg/mL·h at week 16, suggesting drug accumulation over time. The median Cmin and AUC of delamanid, respectively, were 0.17 mcg/mL and 5.1 mcg/mL·h at week 8 and 0.20 mcg/mL and 7.5 mcg/mL·h at week 16. Delay in sputum conversion was observed in patients with drug concentrations lower than the targeted concentration. At weeks 8 and 16, 13 adverse events were observed. Adverse events were resolved through symptomatic treatment. Body mass index was found to be significantly associated with drug-exposure parameters.
CONCLUSIONS: Bedaquiline and delamanid when co-administered exhibit plasma drug levels within the targeted concentrations, showing an exposure-response relationship.

behalf of the International Association of Therapeutic Drug Monitoring and Clinical Toxicology.

DOI: 10.1097/FTD.0000000000001164
PMID: 38161267

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

41. Ten common myths about drug-susceptible TB.

Int J Tuberc Lung Dis. 2024 Jan 1;28(1):61-64. doi: 10.5588/ijtld.23.0373.

Riccardi N(1), Antonello RM(1), Besozzi G(1), Tadolini M(1), Codecasa L(1).

Author information:
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DOI: 10.5588/ijtld.23.0373
PMID: 38178299 [Indexed for MEDLINE]

42. How has the municipal availability of the GeneXpert®MTB/RIF system affected the detection of drug-resistant tuberculosis in Brazil?

Trop Med Int Health. 2024 Jan;29(1):57-62. doi: 10.1111/tmi.13945. Epub 2023 Nov 2.

Aguilar-Jiménez JR(1)(2), Pelissari DM(3), Diaz-Quijano FA(4).

OBJECTIVE: To evaluate the association between the availability of GeneXpert®MTB/RIF in municipalities and the proportion of people who have access to this diagnostic technology for tuberculosis (TB), as well as the resistance detected by the surveillance system in Brazil.
METHODS: We analysed 4998 Brazilian municipalities that reported 432,937 new TB cases between 2015 and 2020. We compared municipalities with and without the availability of GeneXpert®MTB/RIF regarding the effective access to GeneXpert®MTB/RIF diagnosis and the prevalence of detected resistance.
RESULTS: Municipalities with at least one GeneXpert®MTB/RIF system had three times (95% CI 2.9-3.0) the access to diagnostic tests and 80.4% (95% CI 70.6%-90.2%) higher detection of resistance, compared with municipalities without this technology. We estimated that there have been 1890 cases of undetected resistance during this period in the country.
CONCLUSIONS: The availability of GeneXpert®MTB/RIF system in the municipality increased the sensitivity of the surveillance for detecting TB resistance.
PUBLIC HEALTH IMPLICATIONS: It is a priority to strengthen laboratory networks and narrow the gap in access to rapid diagnosis in remote areas to improve the

detection and control of drug-resistant tuberculosis.

DOI: 10.1111/tmi.13945
PMID: 37919228 [Indexed for MEDLINE]

43. Cost-effectiveness of a decentralized care model for managing multi-drug-resistant tuberculosis in low- and middle-income countries: a systematic review protocol.

JBI Evid Synth. 2024 Jan 1;22(1):97-105. doi: 10.11124/JBIES-23-00023.

Mahapatra B(1), Bhattacharya P(1), Karuveettil V(2)(3), John D(1)(4), Khatoon S(1), Mukherjee N(1), Jankiram C(2)(3).

OBJECTIVE: The purpose of this systematic review is to assess the available economic evidence of a decentralized care model compared to a centralized model for treating multi-drug-resistant tuberculosis (MDR-TB) in low- and middle-income countries (LMICs).
INTRODUCTION: Diseases that affect physiological health create a burden on human livelihoods and the economy. There is a lack of studies examining the economic evaluation of MDR-TB across different countries. A preliminary search identified no published or ongoing reviews on MDR-TB in LMICs.
INCLUSION CRITERIA: Studies will be eligible if they include both patients receiving centralized care (ie, care provided by specialist centers through inpatient or outpatient services) and patients receiving decentralized care (ie, care provided by grassroots community workers in peripheral facilities or in the patients' residence) for MDR-TB in LMICs. Eligible studies will report economic evaluations of treatment for MDR-TB.
METHODS: A preliminary search of MEDLINE (PubMed) was undertaken using MeSH terms, such as MDR-TB, economic evaluation, therapeutics, LMICs . Two reviewers will independently screen the titles, abstracts, and full text against the inclusion criteria. Disagreements will be resolved through discussion or with a third reviewer. The JBI checklist for economic evaluations will be utilized to evaluate the methodological quality. Data will be extracted using a modified JBI data extraction form for economic evaluations. The Dominance Ranking Matrix, developed by JBI for economic evaluations, will be used to summarize and compare the results of different types of economic evaluations (cost-effectiveness, cost-benefit analysis, cost-utility analysis, or cost-minimization analysis). Cost per quality-adjusted life year gained and cost per disability-adjusted life year averted will be measures for economic evaluation. The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach will be used to assess the certainty of economic evidence.

REVIEW REGISTRATION: PROSPERO CRD42022368696.

DOI: 10.11124/JBIES-23-00023
PMID: 37779435 [Indexed for MEDLINE]

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

44. Association of indicators of extensive disease and rifampin-resistant tuberculosis treatment outcomes: an individual participant data meta-analysis.

Thorax. 2024 Jan 18;79(2):169-178. doi: 10.1136/thorax-2023-220249.

Campbell JR(1)(2)(3), Brode SK(4)(5), Barry P(6), Bastos ML(7), Bonnet M(8), Guglielmetti L(9), Kempker R(10), Klimuk D(11), Laborín RL(12), Milanov V(13), Singla R(14), Skrahina A(11), Trajman A(3)(15), van der Werf TS(16), Viiklepp P(17), Menzies D(7)(2)(3).

BACKGROUND: Indicators of extensive disease-acid fast bacilli (AFB) smear positivity and lung cavitation-have been inconsistently associated with clinical rifampin-resistant/multidrug-resistant tuberculosis (RR/MDR-TB) outcomes. We evaluated the association of these indicators with end-of-treatment outcomes.
METHODS: We did an individual participant data meta-analysis of people treated for RR/MDR-TB with longer regimens with documented AFB smear and chest radiography findings. We compared people AFB smear-negative without cavities to people: (1) smear-negative with lung cavities; (2) smear-positive without lung cavities and (3) AFB smear-positive with lung cavities. Using multivariable logistic regression accounting for demographic, treatment and clinical factors, we calculated adjusted ORs (aOR) for any unfavourable outcome (death, lost to follow-up, failure/recurrence), and mortality and treatment failure/recurrence alone.
RESULTS: We included 5596 participants; included participants significantly differed from excluded participants. Overall, 774 (13.8%) were AFB smear-negative without cavities, 647 (11.6%) only had cavities, 1424 (25.4%) were AFB smear-positive alone and 2751 (49.2%) were AFB smear-positive with cavities. The median age was 37 years (IQR: 28-47), 3580 (64%) were male and 686 (12.5%) had HIV. Compared with participants AFB smear-negative without cavities, aOR (95% CI) for any unfavourable outcome was 1.0 (0.8 to 1.4) for participants smear-negative with lung cavities, 1.2 (0.9 to 1.5) if smear-positive without cavities and 1.6 (1.3 to 2.0) if AFB smear-positive with lung cavities. Odds were only significantly increased for mortality (1.5, 95% CI 1.1 to 2.1) and failure/recurrence (2.2, 95% CI 1.5 to 3.3) among participants AFB smear-positive with lung cavities.

CONCLUSION: Only the combination of AFB smear-positivity and lung cavitation was associated with unfavourable outcomes, suggesting they may benefit from stronger regimens.

DOI: 10.1136/thorax-2023-220249
PMID: 38135489 [Indexed for MEDLINE]

Conflict of interest statement: Competing interests: None declared.

45. Exploring HIV disease indicators at MDR-TB treatment initiation in South Africa.

Int J Tuberc Lung Dis. 2024 Jan 1;28(1):42-50. doi: 10.5588/ijtld.23.0242.

Geiger K(1), Patil A(2), Bergman A(1), Budhathoki C(1), Heidari O(2), Lowensen K(2), Mthimkhulu N, McNabb KC(1), Mmed NN(3), Ngozo J(4), Reynolds N(1), Farley JE(1).

BACKGROUND: Understanding relationships between HIV and multidrug-resistant TB (MDR-TB) is crucial for ensuring successful MDR-TB outcomes.METHODS: We used a cross-sectional analysis to evaluate sociodemographic and clinical characteristics as correlates of antiretroviral therapy (ART) use, having an HIV viral load (VL) result, and HIV viral suppression in a cross-sectional sample of people with HIV (PWH) and MDR-TB enrolled in a cluster-randomized trial of nurse case management to improve MDR-TB outcomes.RESULTS: Among 1,479 PWH, the mean age was 37.1 years; 809 (54.7%) were male, and 881 (59.6%) were taking ART. Housing location, employment status, and CD4 count differed significantly between those taking vs. those not taking ART. Among the 881 taking ART, 681 (77.3%) had available HIV VL results. Housing location, CD4 count, and prior history of TB differed significantly between those with and without a VL result. Among the 681 with a VL result, 418 (61.4%) were virally suppressed. Age, education level, CD4 count, TB history, housing location, and ART type differed significantly between those with and without viral suppression.CONCLUSION: PWH presenting for MDR-TB treatment with a history of TB, taking a protease inhibitor, or living in a township may risk poor MDR-TB outcomes.

DOI: 10.5588/ijtld.23.0242
PMID: 38178293 [Indexed for MEDLINE]

46. Prevalence, temporal trends and risk factors of drug-resistant TB in Zibo, China, 2018-2021.

Int J Tuberc Lung Dis. 2024 Jan 1;28(1):57-58. doi: 10.5588/ijtld.23.0296.

Yuan S(1), Cui Y(2), Shang Y(3), Su F(1), Liu Y(3), Shi H(1).

DOI: 10.5588/ijtld.23.0296
PMID: 38178294 [Indexed for MEDLINE]

47. Schematic-portfolio of potent anti-microbial scaffolds targeting DNA gyrase: Unlocking ways to overcome resistance.

Int J Biol Macromol. 2024 Jan;256(Pt 2):128402. doi: 10.1016/j.ijbiomac.2023.128402. Epub 2023 Nov 29.

Pakeeraiah K(1), Mal S(1), Mahapatra M(1), Mekap SK(2), Sahu PK(3), Paidesetty SK(4).

Drug development process demands validation of specific drug target impeding the Multi Drug Resistance (MDR). DNA gyrase, as a bacterial target has been in trend for developing newer antibacterial candidates due to its absence in higher eukaryotes. The fluoroquinolones are the leading molecules in the drug discovery pipeline for gyrase inhibition due to its diversity. The fluoroquinolones like levofloxacin and moxifloxacin have been listed in class A drugs for treating MDR. Gatifloxacin and ciprofloxacin also proved its efficacy against MDR TB and MDR enteric fever in adults, whereas nemonoxacin can induce anti-MDR activity of other antibiotics already suggested by studies. Though fluoroquinolones already proved its effectiveness against gyrase, other molecules viz., benzothiazinone, phenyl pyrrolamide, substituted oxadiazoles, triazolopyrimidine, arylbenzothiazole, coumarinyl amino alcohols and ciprofloxacin uracil, can inhibit the target more precisely. The structure-activity-relationships of the different scaffolds along with their synthetic strategies have been deciphered in the current review. Also, the naturally occurring compounds along with their extraction procedure have also been highlighted as potent DNA gyrase inhibitors. In addition to fluoroquinolone, the natural compounds novobiocin and simocyclinone could also inhibit the gyrase, impressively which has been designed with the gyrase structure for better understanding. Herein, ongoing clinical development of some novel drugs possessing triazaacenaphthylenes, spiropyrimidinetriones, and oxazolidinone-quinolone hybrids have been highlighted which could further assist the future generation antibiotic development corroborating gyrase as a potential target against MDR pathogens.

DOI: 10.1016/j.ijbiomac.2023.128402
PMID: 38035955 [Indexed for MEDLINE]

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

48. Drug-induced hypothyroidism in tuberculosis.

Expert Rev Endocrinol Metab. 2024 Jan 19:1-8. doi: 10.1080/17446651.2024.2307525. Online ahead of print.

Quiroz-Aldave JE(1), Durand-Vásquez MDC(1), Gamarra-Osorio ER(2), Concepción-Urteaga LA(3), Pecho-Silva S(4)(5), Rodríguez-Hidalgo LA(3), Concepción-Zavaleta MJ(4).

INTRODUCTION: Adverse reactions to tuberculosis treatment can impact patient adherence and prognosis. Hypothyroidism is a frequent adverse reaction caused using ethionamide, prothionamide, and para-aminosalicylic acid and is often underdiagnosed.
AREAS COVERED: We searched Scielo, Scopus, and EMBASE databases, including 67 articles. Antitubercular drug-induced hypothyroidism has a prevalence of 17%. It occurs after 2 to 3 months of treatment and resolves within 4 to 6 weeks after discontinuation. It is postulated to result from the inhibition of thyroperoxidase function, blocking thyroid hormone synthesis. Symptoms are nonspecific, necessitating individualized thyroid-stimulating hormone measurement for detection. Specific guidelines for management are lacking, but initiation of treatment with levothyroxine, as is customary for primary hypothyroidism, is recommended. Discontinuation of antitubercular drugs is discouraged, as it may lead to unfavorable consequences.
EXPERT OPINION: Antitubercular drug-induced hypothyroidism is more common than previously thought, affecting one in six MDR-TB patients. Despite diagnostic and treatment recommendations, implementation is hindered in low-income countries due to the lack of certified laboratories. New drugs for tuberculosis treatment may affect thyroid function, requiring vigilant monitoring for complications, including hypothyroidism.

DOI: 10.1080/17446651.2024.2307525
PMID: 38258451

49. Anti-tuberculosis activity of morusin: a promising flavonoid from white mulberry.

Int J Tuberc Lung Dis. 2024 Jan 1;28(1):37-41. doi: 10.5588/ijtld.23.0224.

Yildirim K(1), Bozkurt S(2), Basibuyuk HH(3), Coban AY(1).

BACKGROUND: TB has remained a significant public health concern from historical times to the present day. Each year, growing drug resistance problems necessitate the discovery of new drugs and drug precursors for TB treatment. Morusin is an important flavone found in the bark of white mulberry (Morus alba L.) with anti-oxidant, antimicrobial, anti-tumour, anti-inflammatory and antiallergic activity.OBJECTIVE: To determine the anti-TB efficacy of morusin on Mycobacterium tuberculosis strains.DESIGN: Anti-TB efficacy of morusin was tested on H37Ra (American Type Culture Collection [ATCC] 25177), H37Rv (ATCC 27294), ATCC 35822 (isoniazid [INH] resistant), ATCC 35838 (rifampicin [RIF] resistant), and ATCC 35820 (streptomycin [SM] resistant) standard strains and its efficacy was determined using nitrate reductase assay (NRA).RESULTS: The minimum inhibitory concentration (MIC) of morusin was tested in the range of 53.83â-"0.21 Î¼g/ml. The MIC for H37Ra (ATCC 25177), H37Rv (ATCC 27294) and ATCC 35838 (RIF-resistant) strains were found to be 6.72 Î¼g/ml, and this was 13.45 Î¼g/ml for the ATCC 35822 (INHresistant) and ATCC 35820 (SM-resistant) strains.CONCLUSION: To consider morusin as a viable alternative or precursor drug for TB treatment, it is imperative to conduct an exhaustive examination of its mechanism of action and conduct in vitro studies using clinical isolates.

DOI: 10.5588/ijtld.23.0224
PMID: 38178290 [Indexed for MEDLINE]

50. Novel and reported compensatory mutations in rpoABC genes found in drug resistant tuberculosis outbreaks.

Front Microbiol. 2024 Jan 8;14:1265390. doi: 10.3389/fmicb.2023.1265390. eCollection 2023.

Conkle-Gutierrez D(#)(1), Ramirez-Busby SM(#)(1), Gorman BM(1), Elghraoui A(1), Hoffner S(1)(2), Elmaraachli W(3), Valafar F(1).

BACKGROUND: Rifampicin (RIF) is a key first-line drug used to treat tuberculosis, a primarily pulmonary disease caused by Mycobacterium tuberculosis. RIF resistance is caused by mutations in rpoB, at the cost of slower growth and reduced transcription efficiency. Antibiotic resistance to RIF is prevalent despite this fitness cost. Compensatory mutations in rpoABC genes have been shown to alleviate the fitness cost of rpoB:S450L, explaining how RIF resistant strains harbor this mutation can spread so rapidly. Unfortunately, the full set of RIF compensatory mutations is still unknown, particularly those compensating for rarer RIF resistance mutations.
OBJECTIVES: We performed an association study on a globally representative set

of 4,309 whole genome sequenced clinical M. tuberculosis isolates to identify novel putative compensatory mutations, determine the prevalence of known and previously reported putative compensatory mutations, and determine which RIF resistance markers associate with these compensatory mutations.
RESULTS AND CONCLUSIONS: Of the 1,079 RIF resistant isolates, 638 carried previously reported putative and high-probability compensatory mutations. Our strict criteria identified 46 additional mutations in rpoABC for which no strong prior evidence of their compensatory role exists. Of these, 35 have previously been reported. As such, our independent corroboration adds to the mounting evidence that these 35 also carry a compensatory role. The remaining 11 are novel putative compensatory markers, reported here for the first time. Six of these 11 novel putative compensatory mutations had two or more mutation events. Most compensatory mutations appear to be specifically compensating for the fitness loss due to rpoB:S450L. However, an outbreak of 22 closely related isolates each carried three rpoB mutations, the rare RIFR markers D435G and L452P and the putative compensatory mutation I1106T. This suggests compensation may require specific combinations of rpoABC mutations. Here, we report only mutations that met our very strict criteria. It is highly likely that many additional rpoABC mutations compensate for rare resistance-causing mutations and therefore did not carry the statistical power to be reported here. These findings aid in the identification of RIF resistant M. tuberculosis strains with restored fitness, which pose a greater risk of causing resistant outbreaks.

DOI: 10.3389/fmicb.2023.1265390
PMCID: PMC10800992
PMID: 38260909

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

51. Financial burden of tuberculosis diagnosis and treatment for patients in Ethiopia: a systematic review and meta-analysis.

BMC Public Health. 2024 Jan 22;24(1):260. doi: 10.1186/s12889-024-17713-9.

Assefa DG(1), Dememew ZG(2), Zeleke ED(3), Manyazewal T(4), Bedru A(5).

BACKGROUND: Despite the diagnosis and treatment of tuberculosis (TB) given free of charge in many high-burden countries, the costs that patients face in the cascade of care remain a major concern. Here, we aimed to investigate the

financial burden of TB diagnosis and treatment for people with TB in Ethiopia.
METHOD: For this systematic review and meta-analysis, we searched PubMed/MEDLINE, Embase, and Cochrane Center for Clinical Trials from December 1 2022 to 31 June 2023 for articles reporting the cost of diagnosis and treatment for patients regardless of their age with all forms of TB in Ethiopia. Major study outcomes were catastrophic costs, direct (out-of-pocket) pre-diagnosis, medical cost, and post-diagnosis costs, indirect (income loss) costs, coping costs, and total costs. We have used a threshold of 20% to define catastrophic costs. We used random-effects meta-analyses to calculate summary estimates of costs. R-studio software was used for analysis. The study is registered with PROSPERO: CRD42023387687.
RESULT: Twelve studies, with a total of 4792 patients with TB, were included in our analysis. At the 20% threshold of total expenses, 51% of patients (2301 participants from 5 studies, 95% CI: 36-65%, I2 = 97%) faced catastrophic costs due to bacteriologically confirmed drug-sensitive pulmonary TB. Private facility diagnosis, drug-resistance TB, TB-HIV co-infection, hospitalization, and occupation were found to be associated with catastrophic costs. Reduction in the total cost spent by the patients was associated with digital adherence interventions, community-based direct observed therapy, short-course MDR-TB treatment regimens, and active case-finding. Pre-diagnosis costs had a positive correlation with diagnosis delays and the number of facilities visited until diagnosis. Post-diagnosis costs had a positive correlation with rural residence and inpatient treatments.
CONCLUSION: Irrespective of a national policy of free TB service, more than half of TB patients are suffering catastrophic costs due to drug-sensitive pulmonary TB in Ethiopia and most of the patients spend a lot of money during the pre-diagnosis period and intensive phase, but declined drastically over time. Active case-finding, digital adherence interventions, community-based treatment, and comprehensive health insurance coverage have the potential to minimize the financial burden of TB diagnosis and treatment.

DOI: 10.1186/s12889-024-17713-9
PMCID: PMC10804496
PMID: 38254019 [Indexed for MEDLINE]

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

52. Identification and optimization of pyridine carboxamide-based scaffold as a drug lead for Mycobacterium tuberculosis.

Antimicrob Agents Chemother. 2024 Jan 9:e0076623. doi: 10.1128/aac.00766-23.

Online ahead of print.

Singh P(#)(1), Kumar A(#)(1), Sharma P(1), Chugh S(1), Kumar A(2), Sharma N(1), Gupta S(1), Singh M(1), Kidwai S(1), Sankar J(1), Taneja N(1), Kumar Y(1), Dhiman R(2), Mahajan D(1), Singh R(1).

New drugs with novel mechanisms of action are urgently needed to tackle the issue of drug-resistant tuberculosis. Here, we have performed phenotypic screening using the Pathogen Box library obtained from the Medicines for Malaria Venture against Mycobacterium tuberculosis in vitro. We have identified a pyridine carboxamide derivative, MMV687254, as a promising hit. This molecule is specifically active against M. tuberculosis and Mycobacterium bovis Bacillus Calmette-Guérin (M. bovis BCG) but inactive against Enterococcus faecalis, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumanii, Pseudomonas aeruginosa, and Escherichia coli pathogens. We demonstrate that MMV687254 inhibits M. tuberculosis growth in liquid cultures in a bacteriostatic manner. Surprisingly, MMV687254 was as active as isoniazid in macrophages and inhibited M. tuberculosis growth in a bactericidal manner. Mechanistic studies revealed that MMV687254 is a prodrug and that its anti-mycobacterial activity requires AmiC-dependent hydrolysis. We further demonstrate that MMV687254 inhibits M. tuberculosis growth in macrophages by inducing autophagy. In the present study, we have also carried out a detailed structure-activity relationship study and identified a promising novel lead candidate. The identified novel series of compounds also showed activity against drug-resistant M. bovis BCG and M. tuberculosis clinical strains. Finally, we demonstrate that in contrast to MMV687254, the lead molecule was able to inhibit M. tuberculosis growth in a chronic mouse model of infection. Taken together, we have identified a novel lead molecule with a dual mechanism of action that can be further optimized to design more potent anti-tubercular agents.

DOI: 10.1128/aac.00766-23
PMID: 38193667

53. The effect of immunoglobulin G on the humoral immunity in patients with tuberculosis/HIV co-infection.

AIDS Res Hum Retroviruses. 2024 Jan 2. doi: 10.1089/AID.2023.0074. Online ahead of print.

Antonenko P(1), Matsegora N(2), Kaprosh A(3), Vasylyeva T(4), Antonenko K(5).

Previously, an increase in the clinical effectiveness of the anti-tuberculosis therapy (ATT) and antiretroviral therapy (ART) in case of additional IgG administration in patients with multidrug-resistant tuberculosis (MDR-TB)/HIV

coinfection was reported. The aim of this study was to investigate the impact of IgG administration in addition to the standard second-line ATT and ART on the humoral immunity status in patients with MDR-TB/HIV coinfection immune deficiency. Methods. The study involved 52 patients living with HIV with MDR-TB coinfection and CD4+ lymphocyte cells count below 50 cells/μCL. Patients in the control group and the intervention group received the second-line ATT and ART; in addition, patients in the intervention group received immunoglobulin G (IgG) intravenously. The humoral immunity status was evaluated by measurement of IgA, IgE, IgG, IgM in plasma. Results. The standard ATT and ART resulted in a two-step change in humoral immunity: IgM, IgG, IgA and IgE levels gradually increased to a maximal level at the 5-months mark and started to gradually decrease after the 8-months mark. The addition of IgG to the standard therapy resulted in a more steep decrease in the immunoglobulins level in serum, especially IgG, compare to the standard therapy alone, allowing for an earlier initiation of ART in patients in the intervention group.

DOI: 10.1089/AID.2023.0074
PMID: 38164121

54. Associations between air pollutants and acute exacerbation of drug-resistant tuberculosis: evidence from a prospective cohort study.

BMC Infect Dis. 2024 Jan 23;24(1):121. doi: 10.1186/s12879-024-09011-x.

Zhao CN(#)(1), Xu Z(#)(2), Wang P(3), Liu J(4), Wang R(4), Pan HF(5), Bao F(6).

BACKGROUND: Short-term exposure to air pollution may trigger symptoms of drug-resistant tuberculosis (DR-TB) through stimulating lung tissue, damaging tracheobronchial mucosa, the key anti-mycobacterium T cell immune function, and production and release of inflammatory cytokines.
OBJECTIVE: To investigate the association between acute exacerbations of DR-TB and short-term residential exposure to air pollutants (PM10, PM2.5, SO2, NO2, CO and O3) based on a large prospective cohort in Anhui Province, China.
METHOD: Patients were derived from a prospective cohort study of DR-TB in Anhui Province. All DR-TB patients underwent drug-susceptibility testing and prefecture-level reference laboratories confirmed their microbiologies. The case-crossover design was performed to evaluate the association between the risk of acute exacerbations of DR-TB and short-term residential exposure to air pollution.
RESULTS: Short-term NO2 exposure was significantly related to an elevated risk of first-time outpatient visit due to acute exacerbations of DR-TB(relative risk:1.159, 95% confidence interval:1.011 ~ 1.329). Stratification analyses revealed that the relationship between the risk of acute exacerbations and NO2 exposure was stronger in the elderly (age ≥ 65) DR-TB patients, and in

individuals with a history of TB treatment.
CONCLUSIONS: NO2 Exposure was significantly associated with an elevated risk of acute exacerbation of DR-TB in Anhui Province, China.

DOI: 10.1186/s12879-024-09011-x
PMID: 38262983

55. The efficacy and safety of high-dose isoniazid-containing therapy for multidrug-resistant tuberculosis: a systematic review and meta-analysis.

Front Pharmacol. 2024 Jan 8;14:1331371. doi: 10.3389/fphar.2023.1331371. eCollection 2023.

Zhou M(#)(1), Liu AM(#)(2), Yang XB(1), Guan CP(3)(4), Zhang YA(4)(5), Wang MS(3)(4), Chen YL(3)(4).

Objectives: Accumulating evidence are available on the efficacy of high-dose isoniazid (INH) for multidrug-resistant tuberculosis (MDR-TB) treatment. We aimed to perform a systematic review and meta-analysis to compare clinical efficacy and safety outcomes of high-dose INH- containing therapy against other regimes. Methods: We searched the following databases PubMed, Embase, Scopus, Web of Science, CINAHL, the Cochrane Library, and ClinicalTrials.gov. We considered and included any studies comparing treatment success, treatment unsuccess, or adverse events in patients with MDR-TB treated with high-dose INH (>300 mg/day or >5 mg/kg/day). Results: Of a total of 3,749 citations screened, 19 studies were included, accounting for 5,103 subjects, the risk of bias was low in all studies. The pooled treatment success, death, and adverse events of high-dose INH-containing therapy was 76.5% (95% CI: 70.9%-81.8%; I2: 92.03%), 7.1% (95% CI: 5.3%-9.1%; I2: 73.75%), and 61.1% (95% CI: 43.0%-77.8%; I2: 98.23%), respectively. The high-dose INH administration is associated with significantly higher treatment success (RR: 1.13, 95% CI: 1.04-1.22; $p < 0.01$) and a lower risk of death (RR: 0.45, 95% CI: 0.32-0.63; $p < 0.01$). However, in terms of other outcomes (such as adverse events, and culture conversion rate), no difference was observed between high-dose INH and other treatment options (all $p > 0.05$). In addition, no publication bias was observed. Conclusion: In MDR-TB patients, high-dose INH administration is associated with a favorable outcome and acceptable adverse-event profile. Systematic review registration: identifier CRD42023438080.

DOI: 10.3389/fphar.2023.1331371

PMCID: PMC10800833
PMID: 38259285

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

56. Commensal antimicrobial resistance mediates microbiome resilience to antibiotic disruption.

Sci Transl Med. 2024 Jan 17;16(730):eadi9711. doi: 10.1126/scitranslmed.adi9711. Epub 2024 Jan 17.

Bhattarai SK(1)(2), Du M(3)(4), Zeamer AL(1)(2), M Morzfeld B(1)(2), Kellogg TD(1)(2), Firat K(5), Benjamin A(3), Bean JM(3), Zimmerman M(5), Mardi G(6), Vilbrun SC(6), Walsh KF(7)(8), Fitzgerald DW(7), Glickman MS(3)(4), Bucci V(1)(2)(9).

Despite their therapeutic benefits, antibiotics exert collateral damage on the microbiome and promote antimicrobial resistance. However, the mechanisms governing microbiome recovery from antibiotics are poorly understood. Treatment of Mycobacterium tuberculosis, the world's most common infection, represents the longest antimicrobial exposure in humans. Here, we investigate gut microbiome dynamics over 20 months of multidrug-resistant tuberculosis (TB) and 6 months of drug-sensitive TB treatment in humans. We find that gut microbiome dynamics and TB clearance are shared predictive cofactors of the resolution of TB-driven inflammation. The initial severe taxonomic and functional microbiome disruption, pathobiont domination, and enhancement of antibiotic resistance that initially accompanied long-term antibiotics were countered by later recovery of commensals. This resilience was driven by the competing evolution of antimicrobial resistance mutations in pathobionts and commensals, with commensal strains with resistance mutations reestablishing dominance. Fecal-microbiota transplantation of the antibiotic-resistant commensal microbiome in mice recapitulated resistance to further antibiotic disruption. These findings demonstrate that antimicrobial resistance mutations in commensals can have paradoxically beneficial effects by promoting microbiome resilience to antimicrobials and identify microbiome dynamics as a predictor of disease resolution in antibiotic therapy of a chronic infection.

DOI: 10.1126/scitranslmed.adi9711
PMID: 38232140 [Indexed for MEDLINE]

57. Bedaquiline's Safety Profile Monitoring in India: Considerations for Future - A Systematic Review.

Curr Drug Saf. 2024;19(1):24-32. doi: 10.2174/1574886318666230119102506.

Thangaraju P(1), Velmurugan H(1), Yella SST(2).

BACKGROUND: Tuberculosis is still one of the top causes of infection-related death globally. Drug-resistant tuberculosis has a high mortality rate and is still a serious public health concern around the world. The appearance of multidrug-resistant and extensively drug-resistant strains of tuberculosis has increased the need for new therapeutic options against these strains. Most of the drugs used to treat them have been poorly tested and have serious negative effects. Patients with drug-resistant tuberculosis have been fighting for access to experimental medications, particularly bedaquiline.
OBJECTIVE: The study aimed to summarise the existing evidence of bedaquiline's safety on drugresistant tuberculosis treatment outcome and look for bedaquiline-related adverse drug reactions in the Pharmacovigilance Programme of India and World Health Organisation - Uppsala Monitoring Centre database.
METHODS: We searched the PubMed database for relevant studies on the safety profile of bedaquiline used in the treatment of drug-resistant tuberculosis and bedaquiline-related adverse drug reactions in the Pharmacovigilance Programme of India and World Health Organisation - Uppsala Monitoring Centre database published up to April 25, 2022.
RESULTS: A total of 190 abstracts were identified through the Pubmed database. In a list of 157 fulltext eligible articles assessed, 149 were excluded as they did not meet the inclusion criteria. The complete articles of the remaining 8 studies were further evaluated. There were 4 prospective cohorts, 2 retrospective cohorts, and 2 case series.
CONCLUSION: Pharmacovigilance and medication safety monitoring of newer treatments, like bedaquiline, are critical for enhancing treatment support and adherence, especially among drugresistant tuberculosis patients.

DOI: 10.2174/1574886318666230119102506
PMID: 36655524 [Indexed for MEDLINE]

58. Impairments in pulmonary functions in paediatric spinal tuberculosis: a cross-sectional study.

Spine Deform. 2024 Jan;12(1):199-207. doi: 10.1007/s43390-023-00764-0. Epub 2023 Sep 8.

Kolur SS(1), Rathod TN(2), Patil MB(3), Prabhu RM(2), Marathe N(4), Rai AK(2),

Chavan AN(5).

PURPOSE: This study aimed to investigate the impact of vertebral column destruction and kyphotic deformity due to spinal tuberculosis on pulmonary functions in paediatric patients.
METHODS: A cross-sectional study was conducted, involving 30 patients diagnosed with healed spinal tuberculosis, aged 7-18 years. Detailed radiographic measurements, including the level of involvement, kyphosis angle, Spinal Deformity Index (SDI), and drug-resistance status, were compared with various pulmonary function parameters.
RESULTS: The mean age of the study group was 12.8 ± 2.7 years (range 7-17 years), consisting of 11 males and 19 females. Fourteen patients were managed conservatively and 16 were managed operatively. The mean SDI was 5.2 ± 4.7. The mean kyphotic angle was 31.3° ± 25.3. The average number of involved vertebrae was 2.6 ± 1.5. Pulmonary functions were classified as restrictive in 24 patients, normal in 4 patients, obstructive in 1 patient, and mixed in 1 patient. Multidrug-resistant tuberculosis (MDR-TB) was detected in 5 (16.7%) patients, while the remaining 25 (83.3%) patients were sensitive to conventional antitubercular drugs. The correlation coefficients between the percentage reduction in forced vital capacity (FVC) and kyphosis angle, SDI, and number of vertebrae were 0.4 ($p = 0.026$), 0.4 ($p = 0.028$), and 0.19 ($p = 0.295$), respectively. The mean percentage reduction in FVC and total lung capacity (TLC) were 35.8 ± 15.7 and 6.2 ± 2.3, respectively. No significant association was observed between pulmonary functions and drug sensitivity status ($p = 0.074$).
CONCLUSIONS: Paediatric spinal tuberculosis can lead to thoracic insufficiency due to progressive destruction and shortening of the spinal column, spinal growth inhibition, and kyphotic deformity. Management of these cases should focus on promoting normal lung development while ensuring disease resolution and deformity correction. Further research should explore growth conserving or growth guiding systems to address or prevent growth retardation and simultaneously provide spinal stabilization.

DOI: 10.1007/s43390-023-00764-0
PMID: 37682414 [Indexed for MEDLINE]

59. Toxicological Profiling of Potential Shikimate Kinase Inhibitors Against Mycobacterium tuberculosis.

Altern Lab Anim. 2024 Jan;52(1):10-27. doi: 10.1177/02611929231217062. Epub 2023 Dec 14.

Jhangiani A(1), Panda V(1), Sukheja A(1), Thomas S(1), Dusseja P(1), Pandya

S(2), Chintakrindi A(3).

Over the last decade, Mycobacterium tuberculosis has mutated into a putative 'superbug', as treatments against it have failed due to increasing antimicrobial resistance. As a result, the rising incidence of multidrug-resistant tuberculosis (MDR-TB) is posing a significant public health threat, thus, the need to develop effective drugs for MDR-TB has become an urgent priority. To identify new drug candidates for the treatment of MDR-TB, the present study was based on mycobacterial shikimate kinase (MtSK) as the pharmacological target. One hundred potential MtSK inhibitors were identified from literature and database searches to identify compounds that were designed to specifically function as MtSK antagonists. The ADME properties of these compounds were evaluated by using the SwissADME web tool. ProTox-II software was also used to investigate any potential endocrine disrupting effects, mediated through their interaction with oestrogenic and/or androgenic receptors. This study also aimed to predict LD50 values of potential drug candidates that would be active against the standard H37Rv strain of M. tuberculosis, by using the ProTox-II in silico tool. The molecules for which no structural hazard alerts were identified with these software tools were further subjected to molecular docking analyses and molecular dynamic simulations to estimate their ability to interact with the MtSK enzyme. Preliminary results from SwissADME indicated that 30 molecules were drug-like, due to their physicochemical and pharmacokinetic properties. However, subsequent analysis with ToxTree and ProTox-II indicated that only three of these 30 drug-like molecules were suitable for taking forward into further in vitro experiments. This study, which is based on the use of commonly used open-source in silico tools, identified new MtSK ligands for potential use in the development of new drugs for the therapeutic management of tuberculosis. An initial prediction of their safety profile was also generated.

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PMID: 38095084 [Indexed for MEDLINE]

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60. Predictors of Death in Rifampicin Resistant Tuberculosis Patients Treated with the Short Course in Conakry, Guinea.

Am J Trop Med Hyg. 2023 Nov 13;110(1):117-122. doi: 10.4269/ajtmh.23-0190. Print 2024 Jan 3.

Bangoura ST(1)(2)(3), Diallo BD(4)(5), Diaby M(1), Camara A(1)(2), Hounmenou CG(1), Magassouba AS(4), Kadio KJO(1)(2)(3), Vanhems P(6)(7), Touré A(1)(2)(3),

Khanafer N(6)(7).

The emergence of rifampicin-resistant tuberculosis (RR-TB) is a major issue for TB control programs due to high risk of treatment failure and death. The objective of this study was to describe survival and to determine predictors of death in RR-TB patients treated with the short regimen (9-11 months) in the Conakry TB treatment centers. Sociodemographic, clinical, and survival data were collected prospectively between 2016 and 2021 on RR-TB patients in the Department of Pneumo-Phtisiology, the Carrière and the Tombolia TB centers. The Kaplan-Meier method was used to estimate the cumulative incidence of death of patients. The Cox regression model was used to identify the predictors independently associated with death. Of 869 patients, 164 (18.9%) patients died during treatment, 126 of them within 120 days of treatment initiation. The factors associated with death during treatment were as follows: patients treated in the Carrière TB center (adjusted hazard ratio [aHR] = 1.65; 95% CI: 1.06-2.59) and in the Department of Pneumo-Phtisiology (aHR = 3.26; 95% CI: 2.10-5.07), patients ≥ 55 years old (aHR = 4.80; 95% CI: 2.81-8.19), patients with no history of first-line TB treatment (aHR = 1.51; 95% CI: 1.05-2.16), and patients living with HIV (aHR = 2.81; 95% CI: 1.94-4.07). The results of this study can help the national TB control program to reconsider its therapeutic strategy to improve patient care in case of RR-TB. Large prospective clinical studies should be conducted to provide evidence of the impact of such factors like previous history of TB treatment and HIV infection on survival of RR-TB patients.

DOI: 10.4269/ajtmh.23-0190
PMCID: PMC10793011
PMID: 37956449 [Indexed for MEDLINE]

61. Long-term follow-up of persons diagnosed with multidrug-resistant TB in Chennai, India, 2013-2020.

Int J Tuberc Lung Dis. 2024 Jan 1;28(1):54-56. doi: 10.5588/ijtld.23.0272.

Surie D(1), Sathyanarayanan MK(2), Lavanya J(3), Smith JP(1), Shanmugam SK(2), Tamilzhalagan S(2), Selvaraj A(2), Ramesh G(2), Tripathy S(2)(4), Khaparde SD(5), Ho CS(1), Hall-Eidson PJ(1), Ranganathan UDK(2), Selvaraju S(2), Moonan PK(1).

DOI: 10.5588/ijtld.23.0272
PMID: 38178300 [Indexed for MEDLINE]

62. Isoniazid Monoresistance and Antituberculosis Treatment Outcome in Persons With Pulmonary Tuberculosis in Brazil.

Open Forum Infect Dis. 2024 Jan 8;11(1):ofad691. doi: 10.1093/ofid/ofad691. eCollection 2024 Jan.

Araújo-Pereira M(1)(2)(3)(4), Arriaga MB(5), Carvalho ACC(6)(7), Spener-Gomes R(8)(9)(10), Schmaltz CAS(11), Nogueira BMF(2)(3)(4), Figueiredo MC(5), Turner MM(5), Cordeiro-Santos M(8)(9)(12), Rolla VC(11), Sterling TR(5), Andrade BB(1)(2)(3)(4), Kritski AL(6); Regional Prospective Observational Research for Tuberculosis (RePORT)-Brazil Consortium.

Collaborators: Rocha MS, Nascimento V, Santos SRN, Costa AG, Garcia LS, de Sousa Carvalho BK, de Loiola BP, Gomes-Silva A, Ignácio FP, Lourenço MC, Silva EC, Mello M, Souza AB, Benjamin A, Moreira ASR, de Oliveira JG, Cavalcante S, Durovni B, Lapa-E-Silva JR.

BACKGROUND: The high burden of drug-resistant tuberculosis (TB) is a problem to achieve the goals of the End TB Strategy by 2035. Whether isoniazid monoresistance (Hr) affects anti-TB treatment (ATT) outcomes remains unknown in high-burden countries.
METHODS: We evaluated determinants of ATT outcome among pulmonary TB cases reported to the National Notifiable Disease Information System (SINAN) between June 2015 and June 2019, according to drug sensitivity testing (DST) results. Binomial logistic regression models were employed to evaluate whether Hr was associated with an unfavorable ATT outcome: death or failure, compared to cure or treatment completion.
RESULTS: Among 60 804 TB cases reported in SINAN, 21 197 (34.9%) were included in the study. In this database, the frequency of unfavorable outcomes was significantly higher in those with Hr in contrast to isoniazid-sensitive persons with pulmonary TB (9.1% vs 3.05%; P < .001). Using a binomial logistic regression model, Hr was independently associated with unfavorable outcomes (odds ratio, 3.34 [95% confidence interval, 2.06-5.40]; P < .001).
CONCLUSIONS: Hr detected prior to ATT was predictive of unfavorable outcomes at the national level in Brazil. Our data reinforce the need for high-TB-burden countries to prioritize DST to detect Hr. Effective treatment regimens for Hr-TB are needed to improve outcomes.

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PMCID: PMC10785213
PMID: 38221983

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

reported conflicts of interest.

63. Diagnostic efficacy of an optimized nucleotide MALDI-TOF-MS assay for anti-tuberculosis drug resistance detection.

Eur J Clin Microbiol Infect Dis. 2024 Jan;43(1):105-114. doi: 10.1007/s10096-023-04700-y. Epub 2023 Nov 18.

Ou X(#)(1), Song Z(#)(1), Zhao B(#)(1), Pei S(2), Teng C(3), Zheng H(4), He W(5), Xing R(1), Wang Y(1), Wang S(1), Xia H(1), Zhou Y(1), He P(1), Zhao Y(6).

PURPOSE: We aimed at evaluating the diagnostic efficacy of a nucleotide matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF-MS) assay to detect drug resistance of Mycobacterium tuberculosis.
METHODS: Overall, 263 M. tuberculosis clinical isolates were selected to evaluate the performance of nucleic MALDI-TOF-MS for rifampin (RIF), isoniazid (INH), ethambutol (EMB), moxifloxacin (MXF), streptomycin (SM), and pyrazinamide (PZA) resistance detection. The results for RIF, INH, EMB, and MXF were compared with phenotypic microbroth dilution drug susceptibility testing (DST) and whole-genome sequencing (WGS), and the results for SM and PZA were compared with those obtained by WGS.
RESULTS: Using DST as the gold standard, the sensitivity, specificity, and kappa values of the MALDI-TOF-MS assay for the detection of resistance were 98.2%, 98.7%, and 0.97 for RIF; 92.8%, 99%, and 0.90 for INH; 82.4%, 98.0%, and 0.82 for EMB; and 92.6%, 99.5%, and 0.94 for MXF, respectively. Compared with WGS as the reference standard, the sensitivity, specificity, and kappa values of the MALDI-TOF-MS assay for the detection of resistance were 97.4%, 100.0%, and 0.98 for RIF; 98.7%, 92.9%, and 0.92 for INH; 96.3%, 100.0%, and 0.98 for EMB; 98.1%, 100.0%, and 0.99 for MXF; 98.0%, 100.0%, and 0.98 for SM; and 50.0%, 100.0%, and 0.65 for PZA.
CONCLUSION: The nucleotide MALDI-TOF-MS assay yielded highly consistent results compared to DST and WGS, suggesting that it is a promising tool for the rapid detection of sensitivity to RIF, INH, EMB, and MXF.

DOI: 10.1007/s10096-023-04700-y
PMID: 37980301 [Indexed for MEDLINE]

64. Antimicrobial peptides grafted onto the surface of N-acetylcysteine-chitosan nanoparticles can revitalize drugs against clinical isolates of Mycobacterium tuberculosis.

Carbohydr Polym. 2024 Jan 1;323:121449. doi: 10.1016/j.carbpol.2023.121449. Epub 2023 Oct 2.

Primo LMDG(1), Roque-Borda CA(2), Carnero Canales CS(3), Caruso IP(4), de Lourenço IO(4), Colturato VMM(5), Sábio RM(6), de Melo FA(4), Vicente EF(7), Chorilli M(6), da Silva Barud H(5), Barbugli PA(8), Franzyk H(9), Hansen PR(9), Pavan FR(10).

Tuberculosis is caused by Mycobacterium tuberculosis (MTB) and is the leading cause of death from infectious diseases in the World. The search for new antituberculosis drugs is a high priority, since several drug-resistant TB-strains have emerged. Many nanotechnology strategies are being explored to repurpose or revive drugs. An interesting approach is to graft antimicrobial peptides (AMPs) to antibiotic-loaded nanoparticles. The objective of the present work was to determine the anti-MTB activity of rifampicin-loaded N-acetylcysteine-chitosan-based nanoparticles (NPs), conjugated with the AMP Ctx(Ile21)-Ha; against clinical isolates (multi- and extensively-drug resistant) and the H37Rv strain. The modified chitosan and drug-loaded NPs were characterized with respect to their physicochemical stability and their antimycobacterial profile, which showed potent inhibition (MIC values <0.977 μg/mL) by the latter. Furthermore, their accumulation within macrophages and cytotoxicity were determined. To understand the possible mechanisms of action, an in silico study of the peptide against MTB membrane receptors was performed. The results presented herein demonstrate that antibiotic-loaded NPs grafted with an AMP can be a powerful tool for revitalizing drugs against multidrug-resistant M. tuberculosis strains, by launching multiple attacks against MTB. This approach could potentially serve as a novel treatment strategy for various long-term diseases requiring extended treatment periods.

DOI: 10.1016/j.carbpol.2023.121449
PMID: 37940311 [Indexed for MEDLINE]

Conflict of interest statement: Declaration of competing interest All contributing authors declare no conflicts of interest.

65. [Epidemic trend of tuberculosis in adolescents in China, 2000-2019].

Zhonghua Liu Xing Bing Xue Za Zhi. 2024 Jan 10;45(1):78-86. doi: 10.3760/cma.j.cn112338-20230726-00043.

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

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Objective: To analyze the epidemic trend of tuberculosis (TB) in adolescents in China from 2000 to 2019. Methods: We used data from Global Burden of Disease Study 2019 to describe the epidemic trend of TB. The estimated annual percentage changes (EAPC) of the morbidity and mortality were calculated to assess epidemic trends from 2000 to 2019. Results: In 2019, a total of 37 815.670 TB cases and 213.629 deaths were reported in adolescents in China, the morbidity was 25.938/100 000 and the mortality was 0.147/100 000. The cases and deaths of TB in 2019 decreased by 71.84% and 89.90% respectively compared with 2000. In 2019, the incident case number (21 371.747) was 1.30 times higher in male adolescents than in female adolescents (16 443.923), and was 4.11 times higher in age group 15-19 years (30 420.054) than in age group 10-14 years (7 395.616). From 2000 to 2019, the morbidity (EAPC=-3.95, 95%CI: -4.34- -3.55) and mortality (EAPC=-9.18, 95%CI: -9.33- -9.02) of TB in the adolescents showed decreasing trends. The morbidity and mortality of drug-sensitive TB, extensively drug-resistant TB and multidrug-resistant TB all showed decreasing trends. Conclusions: The morbidity and mortality of TB and its subtypes among adolescents in China decreased during 2000-2019. More attention should be paid to male adolescents and adolescents aged 15-19 years due to relatively higher incidence intensity of TB.

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PMID: 38228528 [Indexed for MEDLINE]

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

Acta Paediatr. 2024 Jan 20. doi: 10.1111/apa.17120. Online ahead of print.

Dias JV(1)(2), Varandas L(3)(4)(5), Gonçalves L(3)(6)(7), Kagina BM(8)(9).

DOI: 10.1111/apa.17120
PMID: 38243684

67. "Compassionate use of delamanid in adults and children for drug-resistant tuberculosis: 5-year update."

Eur Respir J. 2024 Jan 18;63(1):2052483. doi: 10.1183/13993003.52483-2020. Print 2024 Jan.

S. Ghosh, L. Breitscheidel, N. Lazarevic, et al.
Eur Respir J 2021; 57: 2002483.

Erratum for
Eur Respir J. 2021 May 20;57(5):

DOI: 10.1183/13993003.52483-2020
PMID: 38237996

Int J Mol Sci. 2024 Jan 13;25(2):1006. doi: 10.3390/ijms25021006.

68. Free Energy Barriers for Passive Drug Transport through the Mycobacterium tuberculosis Outer Membrane: A Molecular Dynamics Study.

Steshin IS(1), Vasyankin AV(1), Shirokova EA(1), Rozhkov AV(1), Livshits GD(1), Panteleev SV(1), Radchenko EV(1)(2), Ignatov SK(1), Palyulin VA(1)(2).

The emergence of multi-drug-resistant tuberculosis strains poses a significant challenge to modern medicine. The development of new antituberculosis drugs is hindered by the low permeability of many active compounds through the extremely strong bacterial cell wall of mycobacteria. In order to estimate the ability of potential antimycobacterial agents to diffuse through the outer mycolate membrane, the free energy profiles, the corresponding activation barriers, and possible permeability modes of passive transport for a series of known antibiotics, modern antituberculosis drugs, and prospective active drug-like molecules were determined using molecular dynamics simulations with the all-atom force field and potential of mean-force calculations. The membranes of different chemical and conformational compositions, density, thickness, and ionization states were examined. The typical activation barriers for the low-mass molecules penetrating through the most realistic membrane model were 6-13 kcal/mol for isoniazid, pyrazinamide, and etambutol, and 19 and 25 kcal/mol for bedaquilin and rifampicin. The barriers for the ionized molecules are usually in the range of 37-63 kcal/mol. The linear regression models were derived from the obtained data, allowing one to estimate the permeability barriers from simple physicochemical parameters of the diffusing molecules, notably lipophilicity and molecular polarizability.

DOI: 10.3390/ijms25021006
PMID: 38256079 [Indexed for MEDLINE]

69. Impaired lung function in adolescents with pulmonary tuberculosis during treatment and following treatment completion.

EClinicalMedicine. 2024 Jan 3;67:102406. doi: 10.1016/j.eclinm.2023.102406.

eCollection 2024 Jan.

van der Zalm MM(1), Jongen VW(1)(2), Swanepoel R(3), Zimri K(1), Allwood B(4), Palmer M(1), Dunbar R(1), Goussard P(5), Schaaf HS(1), Hesseling AC(1), Seddon JA(1)(6).

BACKGROUND: Little is known about post-tuberculosis lung disease in adolescents. We prospectively assessed lung function in adolescents with microbiologically confirmed pulmonary tuberculosis during treatment and after treatment completion.
METHODS: In a prospective study, we enrolled adolescents diagnosed with microbiologically confirmed tuberculosis and healthy tuberculosis-exposed household controls, between October 2020 and July 2021 in Cape Town, South Africa. Spirometry, plethysmography, diffusion capacity lung function tests and 6-min walking test (6MWT) were completed according to international guidelines 2 months into treatment and following treatment completion. Abnormal lung function was defined as abnormal spirometry (z-score < -1.64 for forced expiratory volume in 1 s (FEV1) and/or forced vital capacity (FVC) and/or FEV1/FVC), plethysmography (total lung capacity (TLC) < 80% of predicted, residual volume over TLC of >45%) and/or diffusion capacity (DLCO z-score < -1.64).
FINDINGS: One-hundred adolescents were enrolled; 50 (50%) with tuberculosis and 50 (50%) healthy tuberculosis-exposed controls. Of the 50 adolescents with tuberculosis, ten had multidrug-resistant tuberculosis. Mean age of the group was 14.9 years (SD 2.7), 6 (6.0%) were living with HIV and 9 (9.0%) were previously treated for tuberculosis. Lung function improved over time; during treatment abnormal lung function was found in 76% of adolescents with tuberculosis, compared to 65% after treatment completion. Spirometry indices were lower in adolescents with tuberculosis compared to controls, both at 2 months and after treatment completion. Plethysmography in adolescents with tuberculosis showed that air-trapping was more common during treatment than in controls (12% vs 0%, respectively, p = 0.017); which improved following treatment completion. Adolescents with tuberculosis both during and after treatment completion walked a shorter distance than controls.
INTERPRETATION: Adolescents with tuberculosis have impaired lung function even after treatment completion. It is crucial to include adolescents in trials on the prevention and treatment of tuberculosis-associated respiratory morbidity.
FUNDING: EDCTP, National Institute of Health, Medical Research Council, BMBF.

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PMCID: PMC10796966
PMID: 38261903

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70. Oral Linezolid Induced Early Onset Hepatic Encephalopathy- A Case Report of 65-year Old Diabetic Female.

Curr Drug Saf. 2024;19(1):151-153. doi: 10.2174/1574886318666230417113910.

Upadhyay M(1), Purohit B(1), Pargi P(1).

INTRODUCTION: Linezolid is increasingly utilized to treat gram-positive bacteria that are resistant to other antibiotics like vancomycin-resistant Staphylococcus aureus, methicillinresistant Staphylococcus aureus as well as drug-resistant tuberculosis. It acts by inhibiting protein synthesis in bacteria. Although it is a relatively safe medicine, many reports of hepatotoxicity and neurotoxicity linked to long-term usage have been received but patients with pre-existing risk factors, such as diabetes and alcoholism, may have toxicity even after short-term use of linezolid.
CASE PRESENTATION: Here we are presenting a case of a 65-year-old female with diabetes who developed hepatic encephalopathy after one week of treatment with linezolid prescribed for nonhealing diabetic ulcer after a culture sensitivity test. After the use of linezolid 600 mg BD for 8 days patient developed altered sensorium and breathlessness and had high bilirubin, SGOT, and SGPT. She was diagnosed with hepatic encephalopathy. Linezolid was withdrawn and after 10 days all laboratory parameters for liver function test were improved.
CONCLUSION: Care should be taken when prescribing linezolid in such patients with pre-existing risk factors as they are prone to develop hepatotoxic and neurotoxic adverse effects even after short-term use of linezolid.

DOI: 10.2174/1574886318666230417113910
PMID: 37070438 [Indexed for MEDLINE]