PubMed Open Access Articles

1. **Epidemiological characteristics and risk factors of multidrug-resistant tuberculosis in Luoyang, China.**

Front Public Health. 2023 May 9;11:1117101. doi: 10.3389/fpubh.2023.1117101. eCollection 2023.

Wang Z(1)(2), Hou Y(3), Guo T(1), Jiang T(1), Xu L(2)(3), Hu H(1), Zhao Z(4), Xue Y(2).

OBJECTIVE: We aimed to examine the prevalence of multidrug-resistant tuberculosis (MDR-TB) in Luoyang, China, identify related risk factors, inform clinical practices, and establish standardized anti-tubercular treatment regimens.
METHODS: We conducted a retrospective analysis of high-resolution melting curve (HRM) data from 17,773 cases (2,748 of which were positive) between June 2019 and May 2022 to assess the prevalence of MDR-TB and to identify its associated risk factors.
RESULTS: Between June 2019 and May 2022, out of the 17,773 HRM results, 2,748 were HRM-positive, and 312 were MDR-TB cases. The detection rates for HRM-positive and MDR-TB were 17.0 and 12.1% for males, and 12.4 and 8.2% for females, respectively. The MDR-TB detection rate was higher in the urban areas (14.6%) than in the rural areas (10.6%) and more common among individuals under 51 years of age (14.1%) than those over 50 years of age (9.3%). Notably, the rate of detecting MDR-TB was 18.3% higher in new male patients than in new female patients, which was at 10.6%, and this difference was statistically significant ($p < 0.001$). Moreover, the rate of MDR detection in females who had received anti-tuberculosis treatment (21.3%) was higher than that in males (16.9%). In the multivariate model that considered the results of the sputum smear and detection time, MDR-TB was positively correlated with a history of tuberculosis (TB) treatment, being male, being younger than 51 years, and living in urban areas.
CONCLUSION: Local TB infections are complex and diverse; therefore, more comprehensive monitoring methods are needed to curb the spread of MDR-TB.

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PMCID: PMC10203519
PMID: 37228738 [Indexed for MEDLINE]

Conflict of interest statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could

be construed as a potential conflict of interest.

2. **Global prevalence of drug-resistant tuberculosis: a systematic review and meta-analysis.**

Infect Dis Poverty. 2023 May 25;12(1):57. doi: 10.1186/s40249-023-01107-x.

Salari N(1)(2), Kanjoori AH(3), Hosseinian-Far A(4), Hasheminezhad R(3), Mansouri K(5), Mohammadi M(6).

BACKGROUND: Tuberculosis is a bacterial infectious disease, which affects different parts of a human body, mainly lungs and can lead to the patient's death. The aim of this study is to investigate the global prevalence of drug-resistant tuberculosis using a systematic review and meta-analysis.
METHODS: In this study, the PubMed, Scopus, Web of Science, Embase, ScienceDirect and Google Scholar repositories were systematically searched to find studies reporting the global prevalence of drug-resistant tuberculosis. The search did not entail a lower time limit, and articles published up until August 2022 were considered. Random effects model was used to perform the analysis. The heterogeneity of the studies was examined with the I2 test. Data analysis was conducted within the Comprehensive Meta-Analysis software.
RESULTS: In the review of 148 studies with a sample size of 318,430 people, the I2 index showed high heterogeneity (I2 = 99.6), and accordingly random effects method was used to analyze the results. Publication bias was also examined using the Begg and Mazumdar correlation test which indicated the existence of publication bias in the studies (P = 0.008). According to our meta-analysis, the global pooled prevalence of multi-drug resistant TB is 11.6% (95% CI: 9.1-14.5%).
CONCLUSIONS: The global prevalence of drug-resistant tuberculosis was found to be very high, thus health authorities should consider ways to control and manage the disease to prevent a wider spread of tuberculosis and potentially subsequent deaths.

DOI: 10.1186/s40249-023-01107-x
PMCID: PMC10210422
PMID: 37231463 [Indexed for MEDLINE]

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

3. **Vaccines against Tuberculosis: Where Are We Now?**

Vaccines (Basel). 2023 May 22;11(5):1013. doi: 10.3390/vaccines11051013.

Srivastava S(1), Dey S(2)(3), Mukhopadhyay S(2).

Tuberculosis (TB) is among the top 10 leading causes of death in low-income countries. Statistically, TB kills more than 30,000 people each week and leads to more deaths than any other infectious disease, such as acquired immunodeficiency syndrome (AIDS) and malaria. TB treatment is largely dependent on BCG vaccination and impacted by the inefficacy of drugs, absence of advanced vaccines, misdiagnosis improper treatment, and social stigma. The BCG vaccine provides partial effectiveness in demographically distinct populations and the prevalence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB incidences demands the design of novel TB vaccines. Various strategies have been employed to design vaccines against TB, such as: (a) The protein subunit vaccine; (b) The viral vector vaccine; (c) The inactivation of whole-cell vaccine, using related mycobacteria, (d) Recombinant BCG (rBCG) expressing Mycobacterium tuberculosis (M.tb) protein or some non-essential gene deleted BCG. There are, approximately, 19 vaccine candidates in different phases of clinical trials. In this article, we review the development of TB vaccines, their status and potential in the treatment of TB. Heterologous immune responses generated by advanced vaccines will contribute to long-lasting immunity and might protect us from both drug-sensitive and drug-resistant TB. Therefore, advanced vaccine candidates need to be identified and developed to boost the human immune system against TB.

DOI: 10.3390/vaccines11051013
PMCID: PMC10223910
PMID: 37243117

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

4. **Limited Nosocomial Transmission of Drug-Resistant Tuberculosis, Moldova.**
Emerg Infect Dis. 2023 May;29(5):1046-1050. doi: 10.3201/eid2905.230035.

Noroc E, Chesov D, Merker M, Gröschel MI, Barilar I, Dreyer V, Ciobanu N, Reimann M, Crudu V, Lange C.

Applying whole-genome-sequencing, we aimed to detect transmission events of multidrug-resistant/rifampin-resistant strains of Mycobacterium tuberculosis complex at a tuberculosis hospital in Chisinau, Moldova. We recorded ward, room,

and bed information for each patient and monitored in-hospital transfers over 1 year. Detailed molecular and patient surveillance revealed only 2 nosocomial transmission events.

DOI: 10.3201/eid2905.230035
PMCID: PMC10124655
PMID: 37081601 [Indexed for MEDLINE]

5. **Mycobacterium tuberculosis Intra-Host Evolution Among Drug-Resistant Tuberculosis Patients Failing Treatment.**

Infect Drug Resist. 2023 May 9;16:2849-2859. doi: 10.2147/IDR.S408976. eCollection 2023.

Perumal R(1)(2), Khan A(1), Naidoo K(1)(2), Ngema SL(1), Nandlal L(1)(2), Padayatchi N(1)(2), Dookie N(1)(2).

BACKGROUND: Understanding Mycobacterium tuberculosis (Mtb) intra-host evolution of drug resistance is important for successful drug-resistant tuberculosis (DR-TB) treatment and control strategies. This study aimed to characterise the acquisition of genetic mutations and low-frequency variants associated with treatment-emergent Mtb drug resistance in longitudinally profiled clinical isolates from patients who experienced DR-TB treatment failure.
PATIENTS AND METHODS: We performed deep Whole Genome Sequencing on 23 clinical isolates obtained longitudinally across nine timepoints from five patients who experienced DR-TB treatment failure enrolled in the CAPRISA 020 InDEX study. The minimum inhibitory concentrations (MICs) were established on the BACTEC™ MGIT 960™ instrument on 15/23 longitudinal clinical isolates for eight anti-TB drugs (rifampicin, isoniazid, ethambutol, levofloxacin, moxifloxacin, linezolid, clofazimine, bedaquiline).
RESULTS: In total, 22 resistance associated mutations/variants were detected. We observed four treatment-emergent mutations in two out of the five patients. Emerging resistance to the fluoroquinolones was associated with 16- and 64-fold elevated levofloxacin (2-8 mg/L) and moxifloxacin (1-2 mg/L) MICs, respectively, resulting from the D94G/N and A90V variants in the gyrA gene. We identified two novel mutations associated with elevated bedaquiline MICs (>66-fold): an emerging frameshift variant (D165) on the Rv0678 gene and R409Q variant on the Rv1979c gene present from baseline.
CONCLUSION: Genotypic and phenotypic resistance to the fluoroquinolones and bedaquiline was acquired in two out of five patients who experienced DR-TB treatment failure. Deep sequencing of multiple longitudinal clinical isolates for resistance-associated mutations coupled with phenotypic MIC testing confirmed intra-host Mtb evolution.

DOI: 10.2147/IDR.S408976
PMCID: PMC10182815
PMID: 37193296

Conflict of interest statement: The authors report no conflicts of interest in this work.

6. **Treatment of Infection as a Core Strategy to Prevent Rifampicin-Resistant/Multidrug-Resistant Tuberculosis.**

Pathogens. 2023 May 17;12(5):728. doi: 10.3390/pathogens12050728.

Reuter A(1), Furin J(2).

An estimated 19 million people are infected with rifampicin-resistant/multidrug-resistant strains of tuberculosis worldwide. There is little done to prevent these individuals from becoming sick with RR/MDR-TB, a disease that is associated with high rates of morbidity, mortality, and suffering. There are multiple phase III trials currently being conducted to assess the effectiveness of treatment of infection (i.e., "preventive therapy") for RR/MDR-TB, but their results are likely years away. In the meantime, there is sufficient evidence to support a more comprehensive management of people who have been exposed to RR/MDR-TB so that they can maintain their health. We present a patient scenario and share our experience in implementing a systematic post-exposure management program in South Africa with the goal of inspiring similar programs in other high-burden RR/MDR-TB settings.

DOI: 10.3390/pathogens12050728
PMCID: PMC10222449
PMID: 37242398

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

7. **Metabolomic analysis of Mycobacterium tuberculosis reveals metabolic profiles for identification of drug-resistant tuberculosis.**

Sci Rep. 2023 May 27;13(1):8655. doi: 10.1038/s41598-023-35882-2.

Chaiyachat P(1)(2), Kaewseekhao B(1)(2), Chaiprasert A(3), Kamolwat P(4), Nonghanphithak D(1)(2), Phetcharaburanin J(5), Sirichoat A(1)(2), Ong RT(6),

Faksri K(7)(8).

The detection of pre-extensively (pre-XDR) and extensively drug-resistant tuberculosis (XDR-TB) is challenging. Drug-susceptibility tests for some anti-TB drugs, especially ethambutol (ETH) and ethionamide (ETO), are problematic due to overlapping thresholds to differentiate between susceptible and resistant phenotypes. We aimed to identify possible metabolomic markers to detect Mycobacterium tuberculosis (Mtb) strains causing pre-XDR and XDR-TB. The metabolic patterns of ETH- and ETO-resistant Mtb isolates were also investigated. Metabolomics of 150 Mtb isolates (54 pre-XDR, 63 XDR-TB and 33 pan-susceptible; pan-S) were investigated. Metabolomics of ETH and ETO phenotypically resistant subgroups were analyzed using UHPLC-ESI-QTOF-MS/MS. Orthogonal partial least-squares discriminant analysis revealed distinct separation in all pairwise comparisons among groups. Two metabolites (meso-hydroxyheme and itaconic anhydride) were able to differentiate the pre-XDR and XDR-TB groups from the pan-S group with 100% sensitivity and 100% specificity. In comparisons of the ETH and ETO phenotypically resistant subsets, sets of increased (ETH = 15, ETO = 7) and decreased (ETH = 1, ETO = 6) metabolites specific for the resistance phenotype of each drug were found. We demonstrated the potential for metabolomics of Mtb to differentiate among types of DR-TB as well as between isolates that were phenotypically resistant to ETO and ETH. Thus, metabolomics might be further applied for DR-TB diagnosis and patient management.

DOI: 10.1038/s41598-023-35882-2
PMCID: PMC10224971
PMID: 37244948 [Indexed for MEDLINE]

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

8. **Primary bedaquiline resistance in Karakalpakstan, Uzbekistan.**

Int J Tuberc Lung Dis. 2023 May 1;27(5):381-386. doi: 10.5588/ijtld.22.0536.

Moe S(1), Rekart ML(1), Hernandez D(1), Sholpan A(1), Ismailov A(1), Oluya M(1), Bayniyazova A(1), Zinaida T(2), Nargiza P(3), Gomez-Restrepo C(4), Sitali N(5), Sinha A(6).

BACKGROUND: Bedaquiline (BDQ) is widely used in the treatment of rifampicin-resistant TB (RR-TB). However, resistance to BDQ is now emerging. There are no standardised regimens for BDQ-resistant TB. This study aims to

share experience in managing primary BDQ-resistant TB.METHODS: We performed a retrospective study of patients treated for RR-TB in Karakalpakstan, Uzbekistan, from January 2017 to March 2022. We identified patients with resistance to BDQ with no history of BDQ exposure. We describe baseline characteristics, treatment and follow-up of these patients.RESULTS: Twelve of the 1,930 patients (0.6%) had baseline samples resistant to BDQ with no history of BDQ exposure, 75% (9/12) of whom had been previously treated for TB. Ten (83.3%) were resistant to fluoroquinolones; respectively 66% and 50% had culture conversion by Month 3 and Month 6. The interim treatment outcomes were as follows: unfavourable treatment outcomes (3/12, 25%), favourable outcomes (2/12, 17%); the remaining seven (58%) were continuing treatment.CONCLUSIONS: A large proportion of the cases had previously been treated for TB and had TB resistant to quinolone. Both patients who had not experienced culture conversion by Month 3 had an unfavourable treatment outcome. Therefore, we recommend monthly monitoring of culture status for patients on treatment regimens for BDQ resistance.

CONTEXTE : La bédaquiline (BDQ) est très utilisée dans le traitement de la TB résistante à la rifampicine (RR-TB). Cependant, une résistance à la BDQ est en train d'émerger. Il n'existe aucun schéma thérapeutique standardisé pour la TB résistante à la BDQ. Cette étude vise donc à partager l'expérience de la prise en charge de la TB primaire résistante à la BDQ.
MÉTHODES : Nous avons réalisé une étude rétrospective auprès de patients traites pour RR-TB a Karakalpakstan, Ouzbekistan, de janvier 2017 à mars 2022. Nous avons identifié les patients présentant une résistance à la BDQ sans antécédents d'exposition à la BDQ. Nous décrivons les caractéristiques à l'inclusion, le traitement et le suivi de ces patients.
RÉSULTATS : Douze des 1 930 patients (0,6%) présentaient, a l'inclusion, des échantillons résistants a la BDQ sans antécédents d'exposition a la BDQ, dont 75% (9/12) avaient déjà été traites pour une TB. Dix d'entre eux (83,3%) présentaient une résistance aux fluoroquinolones ; 66% et 50% respectivement ont été associes a une conversion des cultures au Mois 3 et au Mois 6. L'issue intermédiaire du traitement était la suivante : issue défavorable (3/12, 25%), issue favorable (2/12, 17%) et les sept restants (58%) étaient toujours sous traitement.
CONCLUSIONS : Une grande partie des cas avaient déjà été traités pour une TB et présentaient une TB résistante aux quinolones. Les deux patients sans conversion des cultures au Mois 3 ont connu une issue thérapeutique défavorable. Par conséquent, nous recommandons une surveillance mensuelle de l'état des cultures pour les patients sous traitement dans le cadre d'une résistance à la BDQ.

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PMCID: PMC10171487
PMID: 37143220 [Indexed for MEDLINE]

Conflict of interest statement: Conflicts of interest: none declared.

9. **Emergence and evolution of drug-resistant Mycobacterium tuberculosis in eastern China: A six-year prospective study.**

Genomics. 2023 May;115(3):110640. doi: 10.1016/j.ygeno.2023.110640. Epub 2023 May 13.

Wang L(1), Chen B(2), Zhou H(1), Mathema B(3), Chen L(4), Li X(5), Lu Y(5), Liu Z(2), Wang X(6), Wang W(7).

Understanding the emergence and evolution of drug resistance can inform public health intervention to combat tuberculosis (TB). In this prospective molecular epidemiological surveillance study from 2015 to 2021 in eastern China, we prospectively collected whole-genome sequencing and epidemiological data on TB patients. We dissect the ordering of drug resistance mutation acquisition for nine commonly used anti-TB drugs, and we found that the katG S315T mutation first appeared around 1959, followed by rpoB S450L (1969), rpsL L43A (1972), embB M306V (1978), rrs 1401 (1981), fabG1 (1982), pncA (1985) and folC (1988) mutations. GyrA gene mutations appeared after the year of 2000. We observed that the first expansion of Mycobacterium tuberculosis (M.tb) resistance population among eastern China appeared after the introduction of isoniazid, streptomycin and para-amino salicylic acid, and the second expansion after the ethambutol, rifampicin, pyrazinamide, ethionamide and aminoglycosides. We speculate these two expansions are linked with population shift historically. By geospatial analysis, we found drug-resistant isolates migrated within eastern China. With epidemiological data of clonal strains, we observed some strains can evolve continuously in individuals and transmit readily in a population. In conclusion, this study mirrored the emergence and evolution of drug-resistant M.tb in eastern China were linked to the sequence and timing of introduction of anti-TB drugs, and multiple factors may contribute to the resistant population enlarged. To resolve the epidemic of drug-resistant TB, it requires applying anti-TB drugs carefully and/or identifying resistant patients timely to prevent them from developing high-level resistance and transmitting to others.

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PMID: 37187254 [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.

10. **Multidrug-resistant tuberculosis in middle ear: A case report.**

J Clin Tuberc Other Mycobact Dis. 2023 Feb 27;31:100355. doi: 10.1016/j.jctube.2023.100355. eCollection 2023 May.

Cao T(1), Liu X(1), Yang C(1), Mei C(1), Ou J(1), Du R(1).

BACKGROUND: Tuberculosis (TB) continues to be a common disease in developing countries, among which middle ear TB is rare. Furthermore, it is relatively difficult to make an early diagnosis and provide follow-up treatment for middle ear TB. So, it is necessary to report this case for reference and further discussion.
CASE PRESENTATION: We reported 1 case of multidrug-resistant tuberculosis otitis media. TB otitis media is rare in tuberculosis; multidrug-resistant TB otitis media is even more rare. Our paper analyzes the possible causes, imaging, molecular biology, pathology, and clinical manifestations of multidrug-resistant TB otitis media.
CONCLUSION: PCR and DNA molecular biology techniques are highly recommended for the early diagnosis of multidrug-resistant TB otitis media. Early, effective anti-tuberculosis treatment is the guarantee for further recovery for patients with multidrug-resistant TB otitis media.

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PMCID: PMC10011421
PMID: 36926472

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.

11. **Achieving universal access to rapid tuberculosis diagnostics.**

BMJ Glob Health. 2023 May;8(5):e012666. doi: 10.1136/bmjgh-2023-012666.

Ismail N(1), Nathanson CM(2), Zignol M(2), Kasaeva T(2).

DOI: 10.1136/bmjgh-2023-012666
PMID: 37230547 [Indexed for MEDLINE]

Conflict of interest statement: Competing interests: None declared.

12. **Profile and Frequency of Mutations Conferring Drug-Resistant Tuberculosis in the Central, Southeastern and Eastern Ethiopia.**

Infect Drug Resist. 2023 May 12;16:2953-2961. doi: 10.2147/IDR.S408567. eCollection 2023.

Agonafir M(1), Belay G(1), Feleke A(1), Maningi N(2), Girmachew F(3), Reta M(2)(4), Fourie PB(2).

PURPOSE: Advances in molecular tools that assess genes harboring drug resistance mutations have greatly improved the detection and treatment of drug-resistant tuberculosis (DR-TB). This study was conducted to determine the frequency and type of mutations that are responsible for resistance to rifampicin (RIF), isoniazid (INH), fluoroquinolones (FLQs) and second-line injectable drugs (SLIDs) in Mycobacterium tuberculosis (MTB) isolates obtained from culture-positive pulmonary tuberculosis (TB) patients in the central, southeastern and eastern Ethiopia.
PATIENTS AND METHODS: In total, 224 stored culture-positive MTB isolates from pulmonary TB patients referred to Adama and Harar regional TB laboratories between August 2018 and January 2019 were assessed for mutations conferring RIF, INH, FLQs and SLIDs resistance using GenoType®MTBDRplus (MTBDRplus) and GenoType®MTBDRsl (MTBDRsl).
RESULTS: RIF, INH, FLQs and SLIDs resistance-conferring mutations were identified in 88/224 (39.3%), 85/224 (38.0%), 7/77 (9.1%), and 3/77% (3.9%) of MTB isolates, respectively. Mutation codons rpoB S531L (59.1%) for RIF, katG S315T (96.5%) for INH, gyrA A90V (42.1%) for FLQs and WT1 rrs (100%) for SLIDs were observed in the majority of the isolates tested. Over a 10th of rpoB mutations detected in the current study were unknown.
CONCLUSION: In this study, the most common mutations conferring drug resistance to RIF, INH, FLQs were identified. However, a significant proportion of RIF-resistant isolates manifested unknown rpoB mutations. Similarly, although few in number, all SLID-resistant isolates had unknown rrs mutations. To further elucidate the entire spectrum of mutations, tool such as whole-genome sequencing is imperative. Furthermore, the expansion of molecular drug susceptibility testing services is critical for tailoring patient treatment and preventing disease transmission.

DOI: 10.2147/IDR.S408567

PMCID: PMC10187580
PMID: 37201127

Conflict of interest statement: The authors report no conflicts of interest in this work.

13. **Serosal membrane tuberculosis in Iran: A comprehensive review of evidences.**

J Clin Tuberc Other Mycobact Dis. 2023 Feb 23;31:100354. doi: 10.1016/j.jctube.2023.100354. eCollection 2023 May.

Ebrahimzadeh A(1), Pagheh AS(1), Mousavi T(2), Fathi M(3), Moghaddam SGM(4).

Tuberculosis (TB) is among the most common cause of serositis. There are many uncertainties in diagnostic and therapeutic approach to serous membranes tuberculosis. Our aim in the present review is to discuss the regional facilities for timely diagnosis, rapid decision-making and appropriate treatment regarding to serous membranes tuberculosis; with emphasis on situation in Iran. A comprehensive literature searches about the status of serous membranes tuberculosis in Iran were performed in English databases including Google Scholar, Science Direct, Scopus, Pub Med, and Web of Sciences, Persian SID databases, between 2000 and 2021. The main findings of the present review are as follow: a) pleural tuberculosis is more common than pericardial or peritoneal tuberculosis. b) Clinical manifestations are non-specific and so non-diagnostic. c) Smear and culture, PCR and characteristic granulomatous reaction have been used for definitive TB diagnosis by physicians. d) With Adenosine Deaminase Assays and Interferon-Gamma Release Assays in mononuclear dominant fluid, a possible diagnosis of TB is proposed by experienced physicians in Iran. e) In area of endemic for tuberculosis including Iran, a possible diagnosis of TB is enough to begin empirical treatment. f) In patients with uncomplicated tuberculosis serositis, treatment is similar to pulmonary tuberculosis. First line drugs are prescribed unless evidence of MDR-TB is detected. g) The prevalence of drug resistant tuberculosis (MDR-TB) in Iran is between 1% and 6%, and are treated by empirical standardized treatment. h) It is not known whether adjuvant corticosteroids are effective in preventing long term complication. i) Surgery may be recommended for MDR-TB. Tamponade or constrictive pericarditis and intestinal obstruction. In conclusion, it is recommended to consider serosal tuberculosis in patients who have unknown mononuclear dominant effusion and prolonged constitutional symptoms. Experimental treatment with first line anti-TB drugs can be started based on possible diagnostic findings.

DOI: 10.1016/j.jctube.2023.100354
PMCID: PMC9982686
PMID: 36874623

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.

14. **Pyrazinamide-resistant Tuberculosis Obscured From Common Targeted Molecular Diagnostics.**

Drug Resist Updat. 2023 May;68:100959. doi: 10.1016/j.drup.2023.100959. Epub 2023 Apr 6.

Modlin SJ(1), Mansjö M(2), Werngren J(2), Ejike CM(1), Hoffner SE(3), Valafar F(4).

Here, we describe a clinical case of pyrazinamide-resistant (PZA-R) tuberculosis (TB) reported as PZA-susceptible (PZA-S) by common molecular diagnostics. Phenotypic susceptibility testing (pDST) indicated PZA-R TB. Targeted Sanger sequencing reported wild-type PncA, indicating PZA-S TB. Whole Genome Sequencing (WGS) by PacBio and IonTorrent both detected deletion of a large portion of pncA, indicating PZA-R. Importantly, both WGS methods showed deletion of part of the primer region targeted by Sanger sequencing. Repeating Sanger sequencing from a culture in presence of PZA returned no result, revealing that 1) two minority susceptible subpopulations had vanished, 2) the PZA-R majority subpopulation harboring the pncA deletion could not be amplified by Sanger primers, and was thus obscured by amplification process. This case demonstrates how a small susceptible subpopulation can entirely obscure majority resistant populations from targeted molecular diagnostics and falsely imply homogenous susceptibility, leading to incorrect diagnosis. To our knowledge, this is the first report of a minority susceptible subpopulation masking a majority resistant population, causing targeted molecular diagnostics to call false susceptibility. The consequence of such genomic events is not limited to PZA. This phenomenon can impact molecular diagnostics' sensitivity whenever the resistance-conferring mutation is not fully within primer-targeted regions. This can be caused by structural changes of genomic context with phenotypic consequence as we report here, or by uncommon mechanisms of resistance. Such false susceptibility calls promote suboptimal treatment and spread of strains that challenge targeted molecular diagnostics. This motivates development of molecular diagnostics unreliant on primer conservation, and impels frequent WGS surveillance for variants that evade prevailing molecular diagnostics.

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PMID: 37043916 [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.

15. **Bedaquiline and clofazimine resistance in Mycobacterium tuberculosis: an in-vitro and in-silico data analysis.**

Lancet Microbe. 2023 May;4(5):e358-e368. doi: 10.1016/S2666-5247(23)00002-2. Epub 2023 Mar 29.

Sonnenkalb L(1), Carter JJ(2), Spitaleri A(3), Iqbal Z(4), Hunt M(5), Malone KM(4), Utpatel C(1), Cirillo DM(6), Rodrigues C(7), Nilgiriwala KS(8), Fowler PW(9), Merker M(10), Niemann S(11); Comprehensive Resistance Prediction for Tuberculosis: an International Consortium.

Collaborators: Barilar I, Battaglia S, Borroni E, Brandao AP, Brankin A, Cabibbe AM, Carter J, Cirillo DM, Claxton P, Clifton DA, Cohen T, Coronel J, Crook DW, Dreyer V, Earle SG, Escuyer V, Ferrazoli L, Fowler PW, Fu Gao G, 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, Grandjean Lapierre S, Laurenson IF, Letcher B, Lin WH, Liu C, Liu D, Malone KM, Mandal A, Mansjö M, Matias D, Meintjes G, de Freitas Mendes F, Merker M, Mihalic M, Millard J, Miotto P, Mistry N, Moore D, Musser KA, Ngcamu D, Hoang NN, Niemann S, Nilgiriwala KS, Nimmo C, Okozi N, Oliveira RS, Omar SV, Paton N, Peto TE, Watanabe Pinhata JM, Plesnik S, Puyen ZM, Rabodoarivelo MS, Rakotosamimanana N, Rancoita PM, Rathod P, Rodger G, Rodrigues C, Rodwell TC, Roohi E, Santos-Lazaro D, Shah S, Kohl TA, Smith G, Solano W, Spitaleri A, Supply P, Surve U, Tahseen S, Thuong NTT, Thwaites G, Todt K, Trovato A, Utpatel C, Van Rie A, Vijay S, Walker TM, Walker SA, Warren R, Werngren J, Wijkander M, Wilkinson RJ, Wilson DJ, Wintringer P, Yu XX, Yang Y, Zhao Y, Yao SY, Zhu B.

BACKGROUND: Bedaquiline is a core drug for the treatment of multidrug-resistant tuberculosis; however, the understanding of resistance mechanisms is poor, which is hampering rapid molecular diagnostics. Some bedaquiline-resistant mutants are also cross-resistant to clofazimine. To decipher bedaquiline and clofazimine resistance determinants, we combined experimental evolution, protein modelling, genome sequencing, and phenotypic data.

METHODS: For this in-vitro and in-silico data analysis, we used a novel in-vitro evolutionary model using subinhibitory drug concentrations to select bedaquiline-resistant and clofazimine-resistant mutants. We determined bedaquiline and clofazimine minimum inhibitory concentrations and did Illumina and PacBio sequencing to characterise selected mutants and establish a mutation catalogue. This catalogue also includes phenotypic and genotypic data of a global collection of more than 14 000 clinical Mycobacterium tuberculosis complex isolates, and publicly available data. We investigated variants implicated in bedaquiline resistance by protein modelling and dynamic simulations.
FINDINGS: We discerned 265 genomic variants implicated in bedaquiline resistance, with 250 (94%) variants affecting the transcriptional repressor (Rv0678) of the MmpS5-MmpL5 efflux system. We identified 40 new variants in vitro, and a new bedaquiline resistance mechanism caused by a large-scale genomic rearrangement. Additionally, we identified in vitro 15 (7%) of 208 mutations found in clinical bedaquiline-resistant isolates. From our in-vitro work, we detected 14 (16%) of 88 mutations so far identified as being associated with clofazimine resistance and also seen in clinically resistant strains, and catalogued 35 new mutations. Structural modelling of Rv0678 showed four major mechanisms of bedaquiline resistance: impaired DNA binding, reduction in protein stability, disruption of protein dimerisation, and alteration in affinity for its fatty acid ligand.
INTERPRETATION: Our findings advance the understanding of drug resistance mechanisms in M tuberculosis complex strains. We have established an extended mutation catalogue, comprising variants implicated in resistance and susceptibility to bedaquiline and clofazimine. Our data emphasise that genotypic testing can delineate clinical isolates with borderline phenotypes, which is essential for the design of effective treatments.
FUNDING: Leibniz ScienceCampus Evolutionary Medicine of the Lung, Deutsche Forschungsgemeinschaft, Research Training Group 2501 TransEvo, Rhodes Trust, Stanford University Medical Scientist Training Program, National Institute for Health and Care Research Oxford Biomedical Research Centre, Oxford University Hospitals NHS Foundation Trust, Bill & Melinda Gates Foundation, Wellcome Trust, and Marie Skłodowska-Curie Actions.

DOI: 10.1016/S2666-5247(23)00002-2
PMCID: PMC10156607
PMID: 37003285 [Indexed for MEDLINE]

Conflict of interest statement: Declaration of interests AS is the cofounder and

owner of shares in BiKi Technology, which sells the BiKi Life Sciences software suite used in this study's analysis. PWF has received consulting fees from Global Pathogen Analysis Service. All other authors declare no competing interests.

16. **Plasma chemokines CXCL10 and CXCL9 as potential diagnostic markers of drug-sensitive and drug-resistant tuberculosis.**

Sci Rep. 2023 May 6;13(1):7404. doi: 10.1038/s41598-023-34530-z.

Sampath P(#)(1), Rajamanickam A(#)(2), Thiruvengadam K(3), Natarajan AP(4), Hissar S(4), Dhanapal M(1), Thangavelu B(5), Jayabal L(6), Ramesh PM(7), Ranganathan UD(1), Babu S(2), Bethunaickan R(8).

Tuberculosis (TB) diagnosis still remains to be a challenge with the currently used immune based diagnostic methods particularly Interferon Gamma Release Assay due to the sensitivity issues and their inability in differentiating stages of TB infection. Immune markers are valuable sources for understanding disease biology and are easily accessible. Chemokines, the stimulant, and the shaper of host immune responses are the vital hub for disease mediated dysregulation and their varied levels in TB disease are considered as an important marker to define the disease status. Hence, we wanted to examine the levels of chemokines among the individuals with drug-resistant, drug-sensitive, and latent TB compared to healthy individuals. Our results demonstrated that the differential levels of chemokines between the study groups and revealed that CXCL10 and CXCL9 as potential markers of drug-resistant and drug-sensitive TB with better stage discriminating abilities.

DOI: 10.1038/s41598-023-34530-z
PMCID: PMC10163852
PMID: 37149713 [Indexed for MEDLINE]

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

17. **Adverse drug reactions and associated factors in multidrug-resistant tuberculosis: A retrospective review of patient medical records at Mbarara Regional Referral Hospital, Uganda.**

SAGE Open Med. 2023 May 3;11:20503121231171350. doi: 10.1177/20503121231171350. eCollection 2023.

Kushemererwa O(1), Nuwagira E(2), Kiptoo J(1), Yadesa TM(1)(3)(4).
OBJECTIVES: The World Health Organization pragmatic guidelines recommend shorter duration drug regimens with newer, more efficacious agents for treatment of multidrug-resistant tuberculosis. However, adverse drug reactions associated with the use of newer, second-line agents may pose a major barrier to adequate management of multidrug-resistant tuberculosis. We therefore sought to investigate the prevalence and factors associated with adverse drug reactions among patients with multidrug-resistant tuberculosis.
METHODS: We retrospectively reviewed patient medical records at the tuberculosis treatment unit of Mbarara Regional Referral Hospital, between January 2013 and December 2020. Medical records were included in the study, if the patients were aged ⩾18 years, tested sputum positive for multidrug-resistant tuberculosis, with adequate pharmacovigilance data documented. We assessed all documented health-related patient complaints, deranged laboratory values, and clinician suspected adverse drug reactions for scientific/clinical plausibility. Adverse drug reactions were confirmed using published and manufacturer drug references materials. A multidisciplinary clinician team was involved to decide whether to exclude or include a suspected adverse drug reaction.
RESULTS: About 6 in 10 (67.4%; 120/178) patients experienced at least one adverse drug reactions during treatment, of which 18.3%, 14.6%, and 11.4% of adverse drug reactions affected the endocrine/metabolic, otic, and musculoskeletal body systems, respectively. Majority of the adverse drug reactions were probable and had a moderate severity. There was an upward trend in adverse drug reaction incidence between 2015 and 2019. Adverse drug reaction occurrence was associated with previous adverse drug reaction history (adjusted odds ratio = 2.85 (1.08, 7.53 at 95% confidence interval)); however, patients who were underweight (adjusted odds ratio = 0.34 (0.16, 0.69 at 95% confidence interval)) and those treated with bedaquiline-based drug regimens (adjusted odds ratio = 0.2 (0.07, 0.59 at 95% confidence interval)) were less likely to experience an adverse drug reaction.
CONCLUSION: Majority of patients with multidrug-resistant tuberculosis experience at least adverse drug reaction during the course of treatment. The newer standard shorter duration drug regimens (9-12 months) may be associated with intolerable adverse drug reactions that hamper effective management of multidrug-resistant tuberculosis. There is need for more studies to assess the clinical adverse drug reaction burden associated with the implementation of shorter duration regimens.

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PMCID: PMC10161297
PMID: 37152841

Conflict of interest statement: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

18. **Best practices for the care of pregnant people living with TB.**

Int J Tuberc Lung Dis. 2023 May 1;27(5):357-366. doi: 10.5588/ijtld.23.0031.

Maugans C(1), Loveday M(2), Hlangu S(2), Waitt C(3), Van Schalkwyk M(4), van de Water B(5), Salazar-Austin N(6), McKenna L(7), Mathad JS(8), Kalk E(9), Hurtado R(10), Hughes J(11), Eke AC(12), Ahmed S(13), Furin J(14).

BACKGROUND: Each year more than 200,000 pregnant people become sick with TB, but little is known about how to optimize their diagnosis and therapy. Although there is a need for further research in this population, it is important to recognize that much can be done to improve the services they currently receive.METHODS: Following a systematic review of the literature and the input of a global team of health professionals, a series of best practices for the diagnosis, prevention and treatment of TB during pregnancy were developed.RESULTS: Best practices were developed for each of the following areas: 1) screening and diagnosis; 2) reproductive health services and family planning; 3) treatment of drug-susceptible TB; 4) treatment of rifampicin-resistant/multidrug-resistant TB; 5) compassionate infection control practices; 6) feeding considerations; 7) counseling and support; 8) treatment of TB infection/TB preventive therapy; and 9) research considerations.CONCLUSION: Effective strategies for the care of pregnant people across the TB spectrum are readily achievable and will greatly improve the lives and health of this under-served population.

CONTEXTE : Chaque année, environ 200 000 femmes enceintes contractent la TB, mais peu de données sont disponibles pour savoir comment optimiser leur expérience diagnostique et thérapeutique. Si davantage d'études doivent être réalisées dans cette population, beaucoup peut être fait pour améliorer les services dont elle bénéficie.
MÉTHODES : Une série de « bonnes pratiques » pour le diagnostic, la prévention et le traitement de la TB pendant la grossesse a été élaborée en prenant appui sur une revue systématique de la littérature, ainsi que grâce à la contribution d'une équipe internationale de professionnels de la santé travaillant sur les questions relatives à la TB chez les femmes enceintes.
RÉSULTATS : Des bonnes pratiques ont été élaborées dans chacun des domaines suivants : 1) dépistage et diagnostic ; 2) services de santé génésique et planification familiale ; 3) traitement de la TB pharmacosensible ; 4) traitement de la TB résistante à la rifampicine et multirésistante ; 5)

pratiques compatissantes de contrôle des infections ; 6) considérations relatives à l'alimentation ; 7) conseil et soutien ; 8) traitement de l'infection tuberculeuse/traitement préventif de la TB ; et 9) considérations relatives à la recherche.
CONCLUSION : Des stratégies efficaces pour améliorer la prise en charge des femmes enceintes tout au long du spectre de la TB sont à la portée des prestataires et des programmes et sont susceptibles d'améliorer considérablement la vie et la santé de cette population mal prise en charge.

DOI: 10.5588/ijtld.23.0031
PMCID: PMC10171489
PMID: 37143222 [Indexed for MEDLINE]

19. **Bedaquiline resistance pattern in clofazimine-resistant clinical isolates of tuberculosis patients.**

J Glob Antimicrob Resist. 2023 May 3;33:294-300. doi: 10.1016/j.jgar.2023.04.003. Online ahead of print.

Shang Y(1), Chen S(2), Shi W(3), Nie W(3), Jing W(3), Huo F(2), Xue Y(2), Dong L(2), Jiang G(2), Huang H(4), Chu N(5).

OBJECTIVES: Bedaquiline (BDQ) is a potent drug for treating drug-resistant tuberculosis (TB). Here, we analysed the resistance profiles of BDQ in CFZ-resistant clinical isolates and investigated the clinical risk factors of BDQ and CFZ cross/co-resistance.
METHODS: The AlarmarBlue microplate assay was performed to determine the minimum inhibitory concentration (MIC) of the CFZ-resistant Mycobacterium tuberculosis (MTB) clinical isolates to CFZ and BDQ. The clinical characteristics of the respective patients were analysed to explore the possible risk factors of BDQ resistance. The drug-resistance-associated genes including Rv0678, Rv1979c, atpE, pepQ and Rv1453 were sequenced and analysed.
RESULTS: A total of 72 clinical CFZ-resistant MTB isolates were collected; among these, half were identified as BDQ-resistant. The MIC value of BDQ closely correlated with CFZ (Spearman's q = 0.766, P < 0.005). Among the isolates with a MIC of CFZ ≥4 mg/L, 92.31% (12/13) were resistant to BDQ. Pre-XDR and exposure to BDQ or CFZ are the major risk factors for concurrent BDQ resistance. Among the 36 cross/co-resistant isolates, 50% (18/36) had mutations in Rv0678, 8.3% (3/36) had mutations in Rv0678+Rv1453, 5.6% (2/36) had mutations in Rv0678+Rv1979c, 2.8% (1/36) had mutations in Rv0678+Rv1979c+Rv1453, 2.8% (1/36) had mutations in atpE+Rv0678+Rv1453, 2.8% (1/36) had mutations in Rv1979c, and 27.7% (10/36) had no variations in the target genes.
CONCLUSION: Nearly half of the CFZ-resistant isolates were still sensitive to

BDQ, whereas this rate dramatically decreased among patients with pre-XDR TB or those who had been exposed to BDQ or CFZ.

DOI: 10.1016/j.jgar.2023.04.003
PMID: 37142094

20. **Molecular typing and drug sensitivity profiles of M. Tuberculosis isolated from refugees residing in Ethiopia.**

J Clin Tuberc Other Mycobact Dis. 2023 Apr 15;31:100371. doi: 10.1016/j.jctube.2023.100371. eCollection 2023 May.

Meaza A(1)(2), Diriba G(2), Girma M(1), Wondimu A(2), Worku G(1)(3), Medhin G(1), Ameni G(1)(4), Gumi B(1).

BACKGROUND: Refugees in developing countries have poor access to Tuberculosis (TB) care and control services. The understanding of genetic diversity and drug sensitivity patterns of M. tuberculosis (MTB) is important for the TB control program. However, there is no evidence that shows the drug sensitivity profiles and genetic diversity of MTB circulating among refugees residing in Ethiopia. This study aimed to investigate the genetic diversity of MTB strains and lineages, and to identify the drug sensitivity profiles of MTB isolated from refugees residing in Ethiopia.
METHODS: A cross-sectional study was conducted among 68 MTB positive cases isolated from presumptive TB refugees from February to August 2021. Data and samples were collected in the refugee camp clinics and both rapid TB Ag detection and region of difference (RD)-9 deletion typing were used to confirm the MTBs. Drug susceptibility test (DST) and molecular typing were done using Mycobacterium Growth Indicator Tube (MGIT) method and spoligotyping respectively.
RESULTS: DST and spoligotyping results were available for all 68 isolates. The isolates were grouped into 25 spoligotype patterns, which consisted of 1-31 isolates with 36.8% strain diversity. The international shared type (SIT)25 was predominant spoligotype pattern consisting of 31 (45.6%) isolates, followed by SIT24 comprising 5 (7.4%) isolates. Further investigation showed that 64.7% (44/68) of the isolates were belonged to CAS1-Delhi family and 75% (51/68) of the isolates were belonged to lineage(L)-3. Multi-drug resistance (MDR)-TB was observed only in one isolate (1.5%) for first-line anti-TB drugs and the highest level of mono-resistance, 5.9% (4/68), was observed for PZA(Pyrazinamide). Mono-resistance was observed in 2.9 % (2/68) and while 97.0% (66/68) of the MTB positive cases were susceptible to the second-line anti-TB drugs.

CONCLUSION: The findings are useful evidence for the TB screening, treatment and control in refugee populations and surrounding communities in Ethiopia.

DOI: 10.1016/j.jctube.2023.100371
PMCID: PMC10127110
PMID: 37113677

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.

21. **Protocol for a systematic review of long-term physical sequelae and financial burden of multidrug-resistant and extensively drug-resistant tuberculosis.**

PLoS One. 2023 May 15;18(5):e0285404. doi: 10.1371/journal.pone.0285404. eCollection 2023.

Akalu TY(1)(2)(3), Clements ACA(2)(4), Baraki AG(3), Alene KA(1)(2)(3).

INTRODUCTION: Multidrug resistant (MDR) and extensively drug-resistant (XDR) tuberculosis (TB) are major public health threats that are significant causes of physical sequelae and financial consequences for infected people. Treatment for MDR- and XDR-TB are more toxic and take longer duration than for drug-susceptible-TB. As a result, the long-term sequelae are thought to be more common among patients with MDR- and XDR-TB than drug-susceptible-TB, but this is yet to be quantified. Hence, the aim of this systematic review and meta-analysis is to quantify the global burden and types of long-term physical sequelae and financial burden associated with both MDR- and XDR-TB.
METHOD AND ANALYSIS: We will search CINHAL, MEDLINE, Embase, Scopus, and Web of science for studies that report physical and financial sequelae associated with rifampicin-resistant (RR), MDR- and XDR-TB or their treatments. The search will be conducted without time, language, and place restrictions. A random-effects meta-analysis will be conducted to estimate the pooled prevalence of each physical sequela. Heterogeneity will be measured using the Higgins I2 statistics. We will assess publication bias visually using the funnel plot and statistically using Egger's test. Adjustments for publication basis will be made using Tweedie's and Duval Trim and Fill analysis.
ETHICS AND DISSEMINATION: Since the study is based on published evidence, ethics approval is not required. The findings of the systematic review will be presented at various conferences and will be published in a peer-reviewed journal.

PROTOCOL REGISTRATION: The protocol is published in the PROSPERO with registration number CRD42021250909.

DOI: 10.1371/journal.pone.0285404
PMCID: PMC10184907
PMID: 37186609 [Indexed for MEDLINE]

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

22. **Therapeutic Failure and Acquired Bedaquiline and Delamanid Resistance in Treatment of Drug-Resistant TB.**

Emerg Infect Dis. 2023 May;29(5):1081-1084. doi: 10.3201/eid2905.221716.

Millard J, Rimmer S, Nimmo C, O'Donnell M.

New classes of antitubercular drugs, diarylquinolines and nitroimidazoles, have been associated with improved outcomes in the treatment of drug-resistant tuberculosis, but that success is threatened by emerging drug resistance. We report a case of bedaquiline and delamanid resistance in a 55-year-old woman in South Africa with extensively drug-resistant tuberculosis and known HIV.

DOI: 10.3201/eid2905.221716
PMCID: PMC10124645
PMID: 37081529 [Indexed for MEDLINE]

23. **Trends in pulmonary tuberculosis mortality between 1985 and 2018: an observational analysis.**

BMC Pulm Med. 2023 May 26;23(1):184. doi: 10.1186/s12890-023-02458-9.

Singh H(#)(1)(2), Rupal A(#)(2)(3), Al Omari O(2)(4)(5), Jani C(2)(4)(5), Ahmed A(2)(4)(5), Khaliqdina S(4)(5), Walker A(2)(6), Shalhoub J(2)(7)(8), Thomson C(5)(9), Marshall DC(#)(10)(11), Salciccioli JD(#)(2)(5)(12).

BACKGROUND: Pulmonary tuberculosis (TB) is a major source of global morbidity

and mortality. Latent infection has enabled it to spread to a quarter of the world's population. The late 1980s and early 1990s saw an increase in the number of TB cases related to the HIV epidemic, and the spread of multidrug-resistant TB. Few studies have reported pulmonary TB mortality trends. Our study reports and compares trends in pulmonary TB mortality.
METHODS: We utilized the World Health Organization (WHO) mortality database from 1985 through 2018 to analyze TB mortality using the International Classification of Diseases-10 codes. Based on the availability and quality of data, we investigated 33 countries including two countries from the Americas; 28 countries from Europe; and 3 countries from the Western Pacific region. Mortality rates were dichotomized by sex. We computed age-standardized death rates per 100,000 population using the world standard population. Time trends were investigated using joinpoint regression analysis.
RESULTS: We observed a uniform decrease in mortality in all countries across the study period except the Republic of Moldova, which showed an increase in female mortality (+ 0.12 per 100,000 population). Among all countries, Lithuania had the greatest reduction in male mortality (-12) between 1993-2018, and Hungary had the greatest reduction in female mortality (-1.57) between 1985-2017. For males, Slovenia had the most rapid recent declining trend with an estimated annual percentage change (EAPC) of -47% (2003-2016), whereas Croatia showed the fastest increase (EAPC, + 25.0% [2015-2017]). For females, New Zealand had the most rapid declining trend (EAPC, -47.2% [1985-2015]), whereas Croatia showed a rapid increase (EAPC, + 24.9% [2014-2017]).
CONCLUSIONS: Pulmonary TB mortality is disproportionately higher among Central and Eastern European countries. This communicable disease cannot be eliminated from any one region without a global approach. Priority action areas include ensuring early diagnosis and successful treatment to the most vulnerable groups such as people of foreign origin from countries with a high burden of TB and incarcerated population. Incomplete reporting of TB-related epidemiological data to WHO excluded high-burden countries and limited our study to 33 countries only. Improvement in reporting is crucial to accurately identify changes in epidemiology, the effect of new treatments, and management approaches.

DOI: 10.1186/s12890-023-02458-9
PMCID: PMC10224609
PMID: 37237250 [Indexed for MEDLINE]

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

24. **The survival analysis of rifampicin/multidrug-resistant tuberculosis patients**

based on the levels of inflammatory biomarkers: a retrospective cohort study.

Front Cell Infect Microbiol. 2023 May 1;13:1118424. doi: 10.3389/fcimb.2023.1118424. eCollection 2023.

Yu Q(1), Luo H(2), Hu S(1), Sun D(3), Nie Q(4), Yan J(2).

PURPOSE: The development of tuberculosis and inflammatory status are closely related. The aim of this study was to investigate the prognostic value of inflammatory biomarkers in patients with rifampicin/multidrug-resistant tuberculosis (RR/MDR-TB).
PATIENTS AND METHODS: This study recruited 504 patients with RR/MDR-TB from Wuhan Jinyintan Hospital. A total of 348 RR/MDR patients from January 2017 to December 2019 were defined as training set, the rest of patients as validation set. The patients were divided into three-risk degrees according to the levels of inflammatory biomarkers (median, 85th percentile). Kaplan-Meier curve and log-rank test were used to assess survival differences among the groups. Cox proportion risk regression was used to identify risk factors for RR/MDR-TB mortality.
RESULTS: In training set, cox proportion risk regression analysis showed that high age (≥60 years) [OR (95%CI):1.053(1.03188-1.077)], smoking [OR (95%CI):2.206(1.191-4.085)], and bronchiectasia [OR (95%CI):2.867(1.548-5.311)] were prognostic factors for RR/MDR-TB patients. In addition, lower survival rates were observed in high CAR group [OR (95%CI):1.464(1.275-1.681)], high CPR group[OR (95%CI):1.268(1.101-1.459)], high CLR group[OR (95%CI):1.004(1.002-1.005)], high NLR group[OR (95%CI):1.103(1.069-1.139)], high PLR group[OR (95%CI):1.003(1.002-1.004)], and high MLR group[OR (95%CI):3.471(2.188-5.508)].Furthermore, AUCs of age, smoking, bronchiectasia, CAR, CPR, CLR, NLR, PLR, and MLR for predicting mortality in RR/MDR-TB patients were 0.697(95%CI:0.618-0.775), 0.603(95%CI:0.512-0.695), 0.629(95%CI:0.538-0.721), 0.748(95%CI:0.675-0.821, P<0.05), 0.754(95%CI:0.683-0.824, P<0.05), 0.759(95%CI:0.689-0.828, P<0.05), 0.789(95%CI:0.731-0.846, P<0.05), 0.740(95%CI:0.669-0.812, P<0.05), and 0.752(95%CI:0.685-0.819, P<0.05), respectively. Importantly, the AUC of predicting mortality of combination of six inflammatory biomarkers [0.823 (95%CI:0.769-0.876)] is higher than any single inflammatory biomarkers. Additionally, the similar results are also obtained in the validation set.
CONCLUSION: Inflammatory biomarkers could predict the survival status of RR/MDR-TB patients. Therefore, more attention should be paid to the level of inflammatory biomarkers in clinical practice.

DOI: 10.3389/fcimb.2023.1118424

PMCID: PMC10183571
PMID: 37197206 [Indexed for MEDLINE]

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

25. **Treatment cascade for patients with multidrug- or rifampicin-resistant tuberculosis and associated factors with patient attrition in southeastern China: a retrospective cohort study.**

J Infect Public Health. 2023 May 12;16(7):1073-1080. doi: 10.1016/j.jiph.2023.05.012. Online ahead of print.

Chen B(1), Chen X(2), Ren Y(3), Peng Y(2), Wang F(2), Zhou L(2), Xu B(4).

OBJECTIVES: To address gaps in health services for multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB), a treatment cascade model was used to evaluate patient retention and attrition at each successive step required to achieve a successful treatment outcome.
METHODS: From 2015-2018, a four-step treatment cascade model was established in patients with confirmed MDR/RR-TB in southeast China. Step 1: diagnosis of MDR/RR-TB, step 2: Initiation of treatment, step 3: still under treatment at 6 month and step 4: cure or completion of MDR/RR-TB treatment, with each successive step including a gap that shows attrition of patients between steps. The retention and attrition of each step were graphed. Multi-variate logistic regression was carried out to further identify potential factors associated with the attrition.
RESULTS: In the treatment cascade consisting of 1752 MDR/RR-TB patients, the overall patient attrition rate was 55.8% (978/1752), with 28.0% (491/1752), 19.9% (251/1261), and 23.4% (236/1010) of patients attrition in the first, second, and third gap. Factors associated with MDR/RR-TB patients not initiating treatment included age ≥60 years (OR:2.875), and time for diagnosis ≥30 days (OR: 2.653). Patients who were diagnosed with MDR/RR-TB through rapid molecular test (OR: 0.517) and non-migrant residents of Zhejiang Province (OR: 0.273) both exhibited a lower likelihood of attrition during the treatment initiation phase. Meanwhile, old age (OR: 2.190) and non-resident migrants to the province were factors associated with not completing ≥ 6 months of treatment. Old age (OR: 3.883), retreatment (OR: 1.440), and time to diagnosis ≥30 days (OR: 1.626) were factors contributing to poor treatment outcomes.
CONCLUSION: Several programmatic gaps were identified in the MDR/RR-TB treatment cascade. Future policies should provide more comprehensive support for vulnerable populations to improve the care quality at each step.

DOI: 10.1016/j.jiph.2023.05.012
PMID: 37209611

Conflict of interest statement: Declaration of Competing Interest The authors have no competing interests to declare.

26. **Development and validation of a prediction model for unsuccessful treatment outcomes in patients with multi-drug resistance tuberculosis.**

BMC Infect Dis. 2023 May 5;23(1):289. doi: 10.1186/s12879-023-08193-0.

Ma JB(1), Zeng LC(2), Ren F(3), Dang LY(1), Luo H(1), Wu YQ(1), Yang XJ(1), Li R(1), Yang H(4), Xu Y(1).

BACKGROUND: The World Health Organization has reported that the treatment success rate of multi-drug resistance tuberculosis is approximately 57% globally. Although new drugs such as bedaquiline and linezolid is likely improve the treatment outcome, there are other factors associated with unsuccessful treatment outcome. The factors associated with unsuccessful treatment outcomes have been widely examined, but only a few studies have developed prediction models. We aimed to develop and validate a simple clinical prediction model for unsuccessful treatment outcomes in patients with multi-drug resistance pulmonary tuberculosis (MDR-PTB).
METHODS: This retrospective cohort study was performed between January 2017 and December 2019 at a special hospital in Xi'an, China. A total of 446 patients with MDR-PTB were included. Least absolute shrinkage and selection operator (LASSO) regression and multivariate logistic regression were used to select prognostic factors for unsuccessful treatment outcomes. A nomogram was built based on four prognostic factors. Internal validation and leave-one-out cross-validation was used to assess the model.
RESULTS: Of the 446 patients with MDR-PTB, 32.9% (147/446) cases had unsuccessful treatment outcomes, and 67.1% had successful outcomes. After LASSO regression and multivariate logistic analyses, no health education, advanced age, being male, and larger extent lung involvement were identified as prognostic factors. These four prognostic factors were used to build the prediction nomograms. The area under the curve of the model was 0.757 (95%CI 0.711 to 0.804), and the concordance index (C-index) was 0.75. For the bootstrap sampling validation, the corrected C-index was 0.747. In the leave-one-out cross-validation, the C-index was 0.765. The slope of the calibration curve was 0.968, which was approximately 1.0. This indicated that the model was accurate

in predicting unsuccessful treatment outcomes.
CONCLUSIONS: We built a predictive model and established a nomogram for unsuccessful treatment outcomes of multi-drug resistance pulmonary tuberculosis based on baseline characteristics. This predictive model showed good performance and could be used as a tool by clinicians to predict who among their patients will have an unsuccessful treatment outcome.

DOI: 10.1186/s12879-023-08193-0
PMCID: PMC10161636
PMID: 37147607 [Indexed for MEDLINE]

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

27. **Effectiveness of Xpert MTB/RIF and the Line Probe Assay tests for the rapid detection of drug-resistant tuberculosis in the Central African Republic.**

PLOS Glob Public Health. 2023 May 1;3(5):e0001847. doi: 10.1371/journal.pgph.0001847. eCollection 2023.

Farra A(1), Koula K(2), Jolly BL(1), Gando HG(3), Ouarandji LM(3), Mossoro-Kpinde CD(2), Manirakiza A(4), Simelo JP(5), de Dieu Iragena J(6).

The Xpert MTB/RIF and Line Probe Assay (LPA) tests are more and more frequently used in mycobacteria testing laboratories for the rapid diagnosis of multi-drug resistance (MDR-TB). In this study, we demonstrate the effectiveness of these tests in the Central African Republic. Rifampicin resistance cases detected by the Xpert MTB/RIF during the year 2020 are also underwent first- and second-line LPA, and a first-line of drug susceptibility testing (DST) on solid medium and we compared these results. 101 rifampicin resistance cases based on the Xpert MTB/RIF were detected. Mean age was 34 years [16-81]. The 20-40 years age group represented 73.2% and the male-to-female sex ratio was 1.9:1. Patient profiles were dominated by treatment failure cases (40.6%) followed by relapsed cases (30.7%) and new cases (18.8%). These 101 rifampicin resistance were also detected with the first-line LPA and were confirmed by the DST. Similarly, the isoniazid results obtained with the first-line LPA, were confirmed by the DST, giving a concordance of 100% for these antibiotics. Rifampicin resistance were for the most part due to the absence of the WT8 sequence (56%) and the presence of the Mut3 mutation (53.4%). The majority of the isoniazid resistance (94.2%) were due to the Mut1 mutation in the katG gene and 4.2% of the cases involved both the katG gene and the inhA gene promoter with the Mut1 mutation. The

second-line LPA test no resistance to second-line antibiotics. This study demonstrated the effectiveness of the Xpert MTB/RIF and the LPA tests for the rapid diagnosis of MDR-TB in the Central African Republic. However, due to their high cost, these tests have not been extensively deployed in the country. Public authorities and their TB-partners can help make these molecular tests more accessible to fight MDR-TB in the country.

DOI: 10.1371/journal.pgph.0001847
PMCID: PMC10150968
PMID: 37126485

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

28. **Comparing adherence to MDR-TB treatment among patients on self-administered therapy and those on directly observed therapy: non-inferiority randomized controlled trial.**

Trials. 2023 May 12;24(1):326. doi: 10.1186/s13063-023-07314-z.

Wekesa C(1), Sekaggya-Wiltshire C(2), Muyanja SZ(2), Lume I(2), Nabaggala MS(2), Parkes-Ratanshi R(2)(3), Akello SA(4).

BACKGROUND: Adherence is key to the treatment success of multi-drug resistant tuberculosis (MDR-TB) and prevention of community transmission. Directly observed therapy (DOT) is the recommended approach for the management of patients with MDR-TB. Uganda implements a health facility-based DOT approach where all patients diagnosed with MDR-TB report to the nearest private or public health facility for daily observation of ingesting their medicines by a health care provider. Directly observed therapy is very costly for both the patient and health care system. It follows the assumption that MDR TB patients have a history of poor adherence to TB treatment. But only 21% of MDR-TB patients notified globally and 1.4-12% notified in Uganda had been previously treated for TB. The shift to all oral treatment regimen for MDR-TB provides an opportunity for the exploration of self-administered therapy for this group of patients even with use of remotely operated adherence technology. We are conducting a non-inferiority open-label randomized controlled trial to compare adherence to MDR-TB treatment among patients on self-administered therapy (measured by

Medication Events Monitoring System (MEMS) technology) with a control group on DOT.
METHODS: We plan to enrol 164 newly diagnosed MDR-TB patients aged ≥ 8 years from three regional hospitals based in rural and urban Uganda. Patients with conditions that affect their dexterity and ability to operate the MEMS-operated medicine equipment will not be eligible to participate in the trial. Patients are randomized to either of the two study arms: self-administered therapy with adherence being monitored using MEMS technology (intervention arm) or health facility-based DOT (control arm) and will be followed up monthly. Adherence is measured by the number of days the medicine bottle is open to access medication as recorded by the MEMS software in the intervention arm and treatment complaint days as recorded in the TB treatment card in the control arm. The primary outcome is the comparison of adherence rates between the two study arms.
DISCUSSION: The evaluation of self-administered therapy for patients with MDR-TB is important to inform cost-effective management strategies for these patients. The approval of all oral regimens for the treatment of MDR-TB provides an opportunity for innovations such as MEMS technology to support sustainable options for MDR-TB treatment adherence support in low-resource settings.
TRIAL REGISTRATION: Pan African Clinical Trials Registry, Cochrane #PACTR202205876377808. Retrospectively registered on 13 May 2022.

DOI: 10.1186/s13063-023-07314-z
PMCID: PMC10176679
PMID: 37173761 [Indexed for MEDLINE]

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

29. **An analytic feasibility study of the BD MAX™ MDR-TB assay for testing of non-sputum specimens for detection of the Mycobacterium tuberculosis complex (MTBC) and isoniazid (INH) and rifampin (RIF) resistance.**

Diagn Microbiol Infect Dis. 2023 May;106(1):115925. doi: 10.1016/j.diagmicrobio.2023.115925. Epub 2023 Feb 22.

Armstrong D(1), Fisher S(2), Totten M(2), Parrish N(2).

Rapid diagnosis of tuberculosis and drug resistance in extrapulmonary specimens can be challenging. The BD MAX™ multidrug resistant (MDR)-TB assay (BD MAX™) has demonstrated high sensitivity and specificity for the detection of the Mycobacterium tuberculosis complex (MTBC) as well as resistance to INH and Rifampin (RIF) in pulmonary specimens but has not been rigorously assessed in

extrapulmonary samples. We evaluated the diagnostic accuracy of the BD MAX™ assay for the detection of MTBC and drug resistance in extrapulmonary specimens spiked with MTBC from the Johns Hopkins strain collection. A total of 1083 tests were performed across multiple sample types, with an overall percent agreement of 94.8% (795/839) for detection of MTBC and 99% (379/383) and 96.4% (323/335) for determination of INH and RIF resistance-conferring mutations, respectively. The BD MAX™ assay provides same day detection of MTBC and drug-resistance results and could be a beneficial diagnostic test in extrapulmonary sample types.

DOI: 10.1016/j.diagmicrobio.2023.115925
PMID: 36966629 [Indexed for MEDLINE]

Conflict of interest statement: Declaration of Competing Interest All authors confirm they have no competing financial and non-financial interests.

30. **Prognostication of treatment non-compliance among patients with multidrug-resistant tuberculosis in the course of their follow-up: a logistic regression-based machine learning algorithm.**

Front Digit Health. 2023 May 9;5:1165222. doi: 10.3389/fdgth.2023.1165222. eCollection 2023.

Anley DT(1), Akalu TY(2)(3)(4), Dessie AM(1), Anteneh RM(1), Zemene MA(1), Bayih WA(5)(6), Solomon Y(7), Gebeyehu NA(8), Kassie GA(9), Mengstie MA(10), Abebe EC(10), Seid MA(11), Gesese MM(8), Moges N(12), Bantie B(13), Feleke SF(14), Dejenie TA(15), Adella GA(16), Muche AA(2)(17)(18).

INTRODUCTION: Drug compliance is the act of taking medication on schedule or taking medication as prescribed and obeying other medical instructions. It is the most crucial aspect in the treatment of chronic diseases particularly for patients with multidrug-resistant tuberculosis (MDR-TB). Drug non-compliance is the main reason for causing drug resistance and poor treatment outcomes. Hence, developing a risk prediction model by using early obtainable prognostic determinants of non-compliance is vital in averting the existing, unacceptably high level of poor treatment outcomes and reducing drug resistance among MDR-TB patients.
MATERIALS AND METHODS: A retrospective follow-up study was conducted on a total of 517 MDR-TB patients in Northwest Ethiopia. A logistic regression-based machine learning algorithm was used to develop a risk score for the prediction of treatment non-compliance among MDR-TB patients in selected referral hospitals

of Northwest Ethiopia. The data were incorporated in EpiData version 3.1 and exported to STATA version 16 and R version 4.0.5 software for analysis. A simplified risk prediction model was developed, and its performance was reported. It was also internally validated by using a bootstrapping method.
RESULTS: Educational status, registration group (previously treated/new), treatment support, model of care, and khat use were significant prognostic features of treatment non-compliance. The model has a discriminatory power of area under curve (AUC) = 0.79 with a 95% CI of 0.74-0.85 and a calibration test of p-value = 0.5. It was internally validated by using a bootstrapping method, and it has a relatively corrected discriminatory performance of AUC = 0.78 with a 95% CI of 0.73-0.86 and an optimism coefficient of 0.013.
CONCLUSION: Educational status, registration group, treatment supporter, model of care, and khat use are important features that can predict treatment non-compliance of MDR-TB patients. The risk score developed has a satisfactory level of accuracy and good calibration. In addition, it is clinically interpretable and easy to use in clinical practice, because its features are easily ascertainable even at the initial stage of patient enrolment. Hence, it becomes important to reduce poor treatment outcomes and drug resistance.

DOI: 10.3389/fdgth.2023.1165222
PMCID: PMC10203954
PMID: 37228302

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.

31. **Evolution and epidemic success of Mycobacterium tuberculosis in eastern China: evidence from a prospective study.**

BMC Genomics. 2023 May 5;24(1):241. doi: 10.1186/s12864-023-09312-6.

Zhou Z(#)(1), Yi H(#)(2), Zhou Q(#)(3), Wang L(1), Zhu Y(1), Wang W(4)(5), Liu Z(6), Xiong H(1)(7).

BACKGROUND: Lineage distribution of Mycobacterium tuberculosis (Mtb) isolates is strongly associated with geographically distinct human populations, and its transmission can be further impacted by the bacterial genome. However, the epidemic success of Mtb isolates at an individual level was unknown in eastern China. Knowledge regarding the emergence and transmission of Mtb isolates as well as relevant factors may offer a new solution to curb the spread of the

disease. Thus, this study aims to reveal the evolution and epidemic success of Mtb isolates in eastern China.
RESULTS: Of initial 1040 isolates, 997 were retained after removing duplicates and those with insufficient sequencing depth. Of the final samples, 733 (73.52%) were from Zhejiang Province, and 264 (26.48%) were from Shanghai City. Lineage 2 and lineage 4 accounted for 80.44% and 19.56%, with common ancestors dating around 7017 years ago and 6882 years ago, respectively. Sub-lineage L2.2 (80.34%) contributed the majority of total isolates, followed by L4.4 (8.93%) and L4.5 (8.43%). Additionally, 51 (5.12%) isolates were identified to be multidrug-resistant (MDR), of which 21 (29.17%) were pre-extensively drug-resistant (pre-XDR). One clade harboring katG S315T mutation may date back to 65 years ago and subsequently acquired mutations conferring resistance to another five antibiotic drugs. The prevalence of compensatory mutation was the highest in pre-XDR isolates (76.19%), followed by MDR isolates (47.06%) and other drug-resistant isolates (20.60%). Time-scaled haplotypic density analyses suggested comparable success indices between lineage 2 and lineage 4 ($P = 0.306$), and drug resistance did not significantly promote the transmission of Mtb isolates ($P = 0.340$). But for pre-XDR isolates, we found a higher success index in those with compensatory mutations ($P = 0.025$). Mutations under positive selection were found in genes associated with resistance to second-line injectables (whiB6) and drug tolerance (prpR) in both lineage 2 and lineage 4.
CONCLUSIONS: Our study demonstrates the population expansion of lineage 2 and lineage 4 in eastern China, with comparable transmission capacity, while accumulation of resistance mutations does not necessarily facilitate the success of Mtb isolates. Compensatory mutations usually accompany drug resistance and significantly contribute to the epidemiological transmission of pre-XDR strains. Prospective molecular surveillance is required to further monitor the emergence and spread of pre-XDR/XDR strains in eastern China.

DOI: 10.1186/s12864-023-09312-6
PMCID: PMC10161668
PMID: 37147590 [Indexed for MEDLINE]

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

32. **New Horizons in the Diagnosis of Tuberculosis of the Spine: The Role of Whole Genome Sequencing.**

Asian Spine J. 2023 May 17. doi: 10.31616/asj.2022.0247. Online ahead of print.

Ngcelwane M(1), Omar SV(2), Said M(3), Bida M(4).

STUDY DESIGN: Prospective study.
PURPOSE: To evaluate the utility of whole genome sequencing (WGS) in drug resistance testing, lineage of the organisms, and organism- related factors responsible for bacilli settling in the spine.
OVERVIEW OF LITERATURE: The workstream for the diagnosis of tuberculosis (TB) involves isolation and culture of the organism and drug resistance testing using phenotypic methods. Xpert MTB/RIF Ultra is a genetic-based method that detects for Mycobacterium tuberculosis DNA in the rpoB gene. Meanwhile, WGS is a newer genetic-based method that assesses the whole genome of the bacterium. Very few studies have reported the use of WGS for extrapulmonary TB. Herein, we used WGS to diagnose spinal TB.
METHODS: Tissues from 61 patients undergoing surgery for spinal TB underwent histologic examination, Xpert MTB/RIF Ultra, and culture and sensitivity testing. DNA from the cultured bacteria was sent for WGS. The test bacterial genome was compared to a reference strain of pulmonary TB.
RESULTS: Acid-fast bacilli were observed in 9/58 specimens. Meanwhile, histology confirmed TB in all the patients. Bacilli were cultured in 28 patients (48.3%), and the average time to culture was 18.7 days. Xpert MTB/RIF Ultra was positive in 47 patients (85%). WGS was performed in 23 specimens. Overall, 45% of the strains belonged to lineage 2 (East Asian). There was one case of multidrug-resistant TB and two cases of non-tuberculous mycobacteria on WGS. We could not confirm any genomic difference between pulmonary and spinal TB strains.
CONCLUSIONS: Xpert MTB/RIF Ultra of tissues or pus is the investigation of choice when diagnosing spinal TB. Meanwhile, WGS can diagnose multidrug-resistant TB and non-tuberculous mycobacteria more accurately. No mutations were identified in spinal and pulmonary TB bacteria.

DOI: 10.31616/asj.2022.0247
PMID: 37194130

33. **The Association Between Household Financial Burden and Patient Mobility and Their Impact on Loss to Follow-Up Among Multidrug-Resistant Tuberculosis Patients in Guizhou, China.**

Risk Manag Healthc Policy. 2023 May 17;16:909-919. doi: 10.2147/RMHP.S400667. eCollection 2023.

Wang Y(1), Huang Z(2), Chen H(3), Yuan Y(2), McNeil EB(4), Lu X(5), Zhang A(1).

PURPOSE: We aimed to assess the household financial burden due to multidrug-resistant tuberculosis (MDR-TB) treatment and its predictors, examine

its association with patient mobility, and test their impact on patient loss to follow-up (LTFU).
METHODS: A cross-sectional study combining follow-up data collection was conducted at the largest designated MDR-TB hospital in Guizhou. Data were collected from medical records and questionnaires. Household financial burden was measured by the incidence of 2 indicators: catastrophic total costs (CTC) and catastrophic health expenditure (CHE). Mobility was classified as mover or non-mover after the patient's address was verified twice. A multivariate logistic regression model was used to identify associations between variables. Model I and Model II were separated by CHE and CTC.
RESULTS: Out of 180 households, the incidence of CHE and CTC was 51.7% and 80.6%, respectively. Families with low income and patients who were primary income earners were significantly associated with catastrophic costs. 42.8% of patients were movers. Patients from households with CHE (ORadj=2.2, 95% CI: 1.1-4.1) or with CTC (ORadj=2.6, 95% CI: 1.1-6.3) were more likely to move. Finding a job against financial difficulty (58.4%) was the top reason for movers. 20.0% of patients experienced LTFU. Patients from households with catastrophic payments (CHE: ORadj=4.1, 95% CI 1.6-10.5 in Model I; CTC: ORadj=4.8, 95% CI 1.0-22.9 in Model II), patients who were movers (ORadj=6.1, 95% CI 2.5-14.8 in Model I; ORadj=7.4, 95% CI 3.0-18.7 in Model II) and primary income earners (ORadj=2.5, 95% CI: 1.0-5.9 in Model I; ORadj=2.7, 95% CI 1.1-6.6 in Model II) had an increased risk of LTFU.
CONCLUSION: There is a significant association between household financial burden due to MDR-TB treatment and patient mobility in Guizhou. They impact patients' treatment adherence and cause LTFU. Being a primary breadwinner increases the risk for catastrophic household payments and LTFU.

DOI: 10.2147/RMHP.S400667
PMCID: PMC10200133
PMID: 37220483

Conflict of interest statement: The authors report no conflicts of interest in this work.

34. **Bioinformatics Analysis to Uncover the Potential Drug Targets Responsible for Mycobacterium tuberculosis Peptidoglycan and Lysine Biosynthesis.**

Bioinform Biol Insights. 2023 May 10;17:11779322231171774. doi: 10.1177/11779322231171774. eCollection 2023.

Ayu Eka Pitaloka D(1)(2), Izzati A(1), Rafa Amirah S(1), Abdan Syakuran L(3),

Muhammad Irham L(4)(5), Darumas Putri A(6), Adikusuma W(7)(8).

Drug-resistant tuberculosis (TB), which results mainly from the selection of naturally resistant strains of Mycobacterium tuberculosis (MTB) due to mismanaged treatment, poses a severe challenge to the global control of TB. Therefore, screening novel and unique drug targets against this pathogen is urgently needed. The metabolic pathways of Homo sapiens and MTB were compared using the Kyoto Encyclopedia of Genes and Genomes tool, and further, the proteins that are involved in the metabolic pathways of MTB were subtracted and proceeded to protein-protein interaction network analysis, subcellular localization, drug ability testing, and gene ontology. The study aims to identify enzymes for the unique pathways for further screening to determine the feasibility of the therapeutic targets. The qualitative characteristics of 28 proteins identified as drug target candidates were studied. The results showed that 12 were cytoplasmic, 2 were extracellular, 12 were transmembrane, and 3 were unknown. Furthermore, druggability analysis revealed 14 druggable proteins, of which 12 were novel and responsible for MTB peptidoglycan and lysine biosynthesis. The novel targets obtained in this study are used to develop antimicrobial treatments against pathogenic bacteria. Future studies should further shed light on the clinical implementation to identify antimicrobial therapies against MTB.

DOI: 10.1177/11779322231171774
PMCID: PMC10176782
PMID: 37187890

Conflict of interest statement: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

35. **Phenotypic instability of Mycobacterium tuberculosis strains harbouring clinically prevalent drug-resistant mutations.**

Lancet Microbe. 2023 May;4(5):e292. doi: 10.1016/S2666-5247(23)00007-1. Epub 2023 Jan 27.

Chen Y(1), Takiff HE(2), Gao Q(3).

DOI: 10.1016/S2666-5247(23)00007-1
PMID: 36716755 [Indexed for MEDLINE]

Conflict of interest statement: We declare no competing interests. This study was supported by the National Natural Science Foundation of China (grant number 82272376 to QG) and the Shenzhen High-level Hospital Construction Fund (grant number G2022157 to QG).

36. **Evaluation of genetic mutations associated with phenotypic resistance to Fluoroquinolones, Bedaquiline, and Linezolid in clinical Mycobacterium tuberculosis: A systematic review and meta-analysis.**

J Glob Antimicrob Resist. 2023 May 10:S2213-7165(23)00075-9. doi: 10.1016/j.jgar.2023.05.001. Online ahead of print.

An Q(1), Lin R(1), Yang Q(1), Wang C(2), Wang D(3).

OBJECTIVES: The classification of drugs used in multidrug-resistant tuberculosis (MDR-TB) regimens was updated. Group A drugs (fluoroquinolones, bedaquiline (BDQ), and linezolid (LZD) are crucial drugs for the control of MDR-TB. Molecular drug resistance assays could facilitate the effective use of Group A drugs.
METHODS: We summarized the evidence implicating specific genetic mutations for Group A drugs. We searched PubMed, Embase, MEDLINE, and Cochrane library for studies published from the inception of each database until July 1, 2022. Using a random-effects model, we calculated the odds ratios (ORs) and 95% confidence intervals (CIs) as our measures of association.
RESULTS: A total of 5,001 clinical isolates were included in 47 studies. The mutations of gyrA A90V, D94G, D94N, and D94Y were significantly associated with an increased risk of levofloxacin (LFX)-resistant isolates. In addition, the mutations of gyrA G88C, A90V, D94G, D94H, D94N, and D94Y were significantly associated with an increased risk of having moxifloxacin (MFX)-resistant isolates. Only in a single study, the majority of gene locus (n=126, 90.65%) observed to have unique mutations in atpE, Rv0678, mmpL5, pepQ, and Rv1979c in BDQ-resistant isolates. The most common mutations occurred at four sites in the rrl gene (g2061t, g2270c, g2270t, and g2814t) and one site in rplC (C154R) in LZD-resistant isolates. Our meta-analysis demonstrated no mutations associated with BDQ- or LZD-resistant phenotypes.
CONCLUSIONS: The mutations detected by rapid molecular assay are correlated with phenotypic resistance to LFX and MFX. The absence of mutation-phenotype associations for BDQ and LZD hindered the development of a rapid molecular assay.

DOI: 10.1016/j.jgar.2023.05.001

PMID: 37172764

Conflict of interest statement: Declaration of Competing Interest None declared.

37. **Digital adherence technologies to improve tuberculosis treatment outcomes in China: a cluster-randomised superiority trial.**

Lancet Glob Health. 2023 May;11(5):e693-e703. doi: 10.1016/S2214-109X(23)00068-2.

Liu X(1), Thompson J(2), Dong H(3), Sweeney S(4), Li X(1), Yuan Y(5), Wang X(6), He W(7), Thomas B(8), Xu C(1), Hu D(1), Vassall A(4), Huan S(9), Zhang H(1), Jiang S(1), Fielding K(2), Zhao Y(10).

Comment in
Lancet Glob Health. 2023 May;11(5):e634-e635.

BACKGROUND: Drug-sensitive tuberculosis treatment requires 6 months of therapy, so adherence problems are common. Digital adherence technologies might improve tuberculosis treatment outcomes. We aimed to evaluate the effect of a daily reminder medication monitor, monthly review of adherence data by the health-care provider, and differentiated care for patients with adherence issues, on tuberculosis treatment adherence and outcomes.
METHODS: We did a cluster-randomised superiority trial across four prefectures in China. 24 counties or districts (clusters) were randomly assigned (1:1) to intervention or control groups. We enrolled patients aged 18 years or older with GeneXpert-positive, rifampicin-sensitive pulmonary tuberculosis, who were receiving daily fixed-dose combination treatment. Patients in the intervention group received a medication monitor for daily drug-dosing reminders, monthly review of adherence data by health-care provider, and management of poor adherence; and patients in the control group received routine care (silent-mode monitor-measured adherence). Only the independent endpoints review committee who assessed endpoint data for some participants were masked to study group assignment. Patients were followed up (with sputum solid culture) at 12 and 18 months. The primary outcome was a composite of death, loss to follow-up, treatment failure, switch to multidrug-resistant tuberculosis treatment, or tuberculosis recurrence by 18 months from treatment start, analysed in the intention-to-treat population. Analysis accounted for study design with multiple imputation for the primary outcome. This trial is now complete and is registered with ISRCTN, 35812455.
FINDINGS: Between Jan 26, 2017, and April 3, 2019, 15 257 patients were assessed for eligibility and 3074 were enrolled, 2686 (87%) of whom were included in the intention-to-treat population. 1909 (71%) of 2686 patients were male, 777 (29%)

were female, and the median age was 44 years (IQR 29-58). By 18 months from treatment start, using multiple imputation for missing outcomes, 239 (16% [geometric mean of cluster-level proportion]) of 1388 patients in the control group and 224 (16%) of 1298 in the intervention group had a primary composite outcome event (289 [62%] of 463 events were loss to follow-up during treatment and 42 [9%] were tuberculosis recurrence). The intervention had no effect on risk of the primary composite outcome (adjusted risk ratio 1·01, 95% CI 0·73-1·40).
INTERPRETATION: Our digital medication monitor intervention had no effect on unfavourable outcomes, which included loss to follow-up during treatment, tuberculosis recurrence, death, and treatment failure. There was a failure to change patient management following identification of treatment non-adherence at monthly reviews. A better understanding of adherence patterns and how they relate to poor outcomes, coupled with a more timely review of adherence data and improved implementation of differentiated care, may be required.
FUNDING: Bill & Melinda Gates Foundation.

DOI: 10.1016/S2214-109X(23)00068-2
PMCID: PMC10126227
PMID: 37061308 [Indexed for MEDLINE]

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

38. **Development of low-cost, weight-adjustable clofazimine mini-tablets for treatment of tuberculosis in pediatrics.**

Eur J Pharm Sci. 2023 May 18;187:106470. doi: 10.1016/j.ejps.2023.106470. Online ahead of print.

Warnken Z(1), Trementozzi A(1), Martins PP(1), Parekh J(1), Koleng JJ(1), Smyth HDC(2), Brunaugh A(3).

Clofazimine (CFZ) is an important component of the World Health Organization's (WHO) recommended all-oral drug regimen for treatment of multi-drug resistant tuberculosis (MDR-TB). However, the lack of a dividable oral dosage form has limited the use of the drug in pediatric populations, who may require lowering of the dose to reduce the likelihood of adverse drug events. In this study, pediatric-friendly CFZ mini-tablets were prepared from micronized powder via

direct compression. Rapid disintegration and maximized dissolution in GI fluids was achieved using an iterative formulation design process. Pharmacokinetic (PK) parameters of the optimized mini-tablets were obtained in Sprague-Dawley rats and compared against an oral suspension of micronized CFZ particles to examine the effect of processing and formulation on the oral absorption of the drug. Differences in maximum concentration and area under the curve between the two formulations were non-significant at the highest dosing level tested. Variability between rats prevented bioequivalence from being determined according to guidelines outlined by the Food and Drug Administration (FDA). These studies provide an important proof-of-concept for an alternative, low-cost formulation and processing approach for the oral delivery of CFZ in manner that is suitable for children as young as 6 months of age.

DOI: 10.1016/j.ejps.2023.106470
PMID: 37207942

Conflict of interest statement: Declaration of Competing Interest Z.W., A.T., P.M., J.P., and A.B., were employees of Via Therapeutics during the period in which data was generated for the manuscript. A.B. receives consulting fees and has equity and stock ownership in Cloxero Therapeutics, Inc. J.K. receives consulting fees and has equity and stock ownership in Via Therapeutics, LLC and Cloxero Therapeutics, Inc., receives consulting fees and has stock ownership in TFF Pharmaceuticals, Inc. and receives consulting fees and has equity in AlphaVektor, LLC. H.S. receives consulting fees and has equity and stock ownership in Via Therapeutics, CloXero Therapeutics, and Nob Hill Therapeutics, and receives consulting fees from the Institute for Advanced Clinical Trials for Children. Patent applications (PCT/US2018/053,947 and US 63/433,438) pertaining to the results presented in this paper have been filed by the University of Texas at Austin and Via Therapeutics, LLC.

39. **Quantitative (1)H Nuclear Magnetic Resonance Assay for the Rapid Detection of Pyrazinamide Resistance in Mycobacterium tuberculosis from Sputum Samples.**

J Clin Microbiol. 2023 May 23;61(5):e0152222. doi: 10.1128/jcm.01522-22. Epub 2023 Apr 18.

Lopez JM(1), Zimic M(2), Vallejos K(2), Sevilla D(1), Quispe-Carbajal M(1), Roncal E(2), Rodríguez J(2), Rodríguez J(2), Antiparra R(2), Arteaga H(2), Gilman RH(3), Maruenda H(1), Sheen P(2).

Tuberculosis (TB), caused by Mycobacterium tuberculosis, is one of the 10

leading killer diseases in the world. At least one-quarter of the population has been infected, and there are 1.3 million deaths annually. The emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains challenges TB treatments. One of the drugs widely used in first- and second-line regimens is pyrazinamide (PZA). Statistically, 50% of MDR and 90% of XDR clinical strains are resistant to PZA, and recent studies have shown that its use in patients with PZA-resistant strains is associated with higher mortality rates. Therefore, the is an urgent need for the development of an accurate and efficient PZA susceptibility assay. PZA crosses the M. tuberculosis membrane and is hydrolyzed to its active form, pyrazinoic acid (POA), by a nicotinamidase encoded by the pncA gene. Up to 99% of clinical PZA-resistant strains have mutations in this gene, suggesting that this is the most likely mechanism of resistance. However, not all pncA mutations confer PZA resistance, only the ones that lead to limited POA production. Therefore, susceptibility to PZA may be addressed simply by its ability to form, or not, POA. Here, we present a nuclear magnetic resonance method to accurately quantify POA directly in the supernatant of sputum cultures collected from TB patients. The ability of the clinical sputum culture to hydrolyze PZA was determined, and the results were correlated with the results of other biochemical and molecular PZA drug susceptibility assays. The excellent sensitivity and specificity values attained suggest that this method could become the new gold standard for the determination of PZA susceptibility.

DOI: 10.1128/jcm.01522-22
PMCID: PMC10204627
PMID: 37071032 [Indexed for MEDLINE]

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

40. **Definitive outcomes in patients with rifampicin-resistant tuberculosis treated in Niger from 2012 to 2019: A retrospective cohort study.**

Int Health. 2023 May 2;15(3):258-264. doi: 10.1093/inthealth/ihac016.

Souleymane MB(1), Decroo T(2)(3), Mamadou S(4), Soumana A(5), Lawan IM(1), Gagara-Issoufou A(4), Adehossi E(4), Ortuño-Gutiérrez N(6), Lynen L(2), Rigouts L(2)(7), de Jong BC(2), Van Deun A(8), Piubello A(1)(6).

BACKGROUND: Outcomes of retreatment for rifampicin-resistant tuberculosis (RR-TB) are rarely reported. We report 'definitive outcomes' after a cascade approach to RR-TB treatment. After a bacteriologically adverse outcome for the 9-months fluoroquinolone-based Short Treatment Regimen (STR), patients were retreated with a bedaquiline-based regimen (BDQ-regimen).

METHODS: A Retrospective cohort study of RR-TB patients treated with the STR during 2012-2019 and retreated with a BDQ-regimen in case of failure or relapse was conducted. Definitive relapse-free cure took into account BDQ-regimen outcomes.
RESULTS: Of 367 patients treated with the STR, 20 (5.4%) experienced failure or relapse. Out of these 20 patients, 14 started a BDQ-regimen, of whom none experienced failure or relapse. Definitive end of treatment outcomes of STR after revising with third-line BDQ-regimen outcomes, 84.7% (311/367) were cured relapse-free, 10.6% (39/367) died during treatment and 3.0% (11/367) were lost to follow-up during treatment with either the STR or BDQ-regimen. Six patients (1.6%; 6/367) with STR failure/relapse died before starting a BDQ-regimen. No patient had definitive treatment failure or relapse and remained without treatment.
CONCLUSIONS: If fluoroquinolone resistance is excluded or rare, it is beneficial to use fluoroquinolone as the core drug for a first RR-TB treatment regimen and to safeguard bedaquiline for those in need of retreatment.

DOI: 10.1093/inthealth/ihac016
PMCID: PMC10153560
PMID: 35420123 [Indexed for MEDLINE]

Conflict of interest statement: None declared.

41. **The mutational signatures of poor treatment outcomes on the drug-susceptible Mycobacterium tuberculosis genome.**

Elife. 2023 May 3;12:e84815. doi: 10.7554/eLife.84815.

Chen Y(1)(2), Jiang Q(3), Peierdun M(4), Takiff HE(5), Gao Q(1)(2).

Update of
doi: 10.1101/2022.11.20.517260.

Drug resistance is a known risk factor for poor tuberculosis (TB) treatment outcomes, but the contribution of other bacterial factors to poor outcomes in drug-susceptible TB is less well understood. Here, we generate a population-based dataset of drug-susceptible Mycobacterium tuberculosis (MTB) isolates from China to identify factors associated with poor treatment outcomes. We analyzed whole-genome sequencing (WGS) data of MTB strains from 3196 patients, including 3105 patients with good and 91 patients with poor treatment

outcomes, and linked genomes to patient epidemiological data. A genome-wide association study (GWAS) was performed to identify bacterial genomic variants associated with poor outcomes. Risk factors identified by logistic regression analysis were used in clinical models to predict treatment outcomes. GWAS identified fourteen MTB fixed mutations associated with poor treatment outcomes, but only 24.2% (22/91) of strains from patients with poor outcomes carried at least one of these mutations. Isolates from patients with poor outcomes showed a higher ratio of reactive oxygen species (ROS)-associated mutations compared to isolates from patients with good outcomes (26.3% vs 22.9%, t-test, p=0.027). Patient age, sex, and duration of diagnostic delay were also independently associated with poor outcomes. Bacterial factors alone had poor power to predict poor outcomes with an AUC of 0.58. The AUC with host factors alone was 0.70, but increased significantly to 0.74 (DeLong's test, p=0.01) when bacterial factors were also included. In conclusion, although we identified MTB genomic mutations that are significantly associated with poor treatment outcomes in drug-susceptible TB cases, their effects appear to be limited.

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PMID: 37133242 [Indexed for MEDLINE]

Conflict of interest statement: YC, QJ, MP, HT, QG No competing interests declared

42. **Epidemiology of Nontuberculous Mycobacteria in Nanjing and MAB_0540 Mutations Associated with Clofazimine Resistance in Mycobacterium abscessus.**

Infect Drug Resist. 2023 May 6;16:2751-2764. doi: 10.2147/IDR.S408986. eCollection 2023.

Zhang R(1), Luo S(1), Wang N(1), Zhang H(2), Wu X(1).

BACKGROUND: Nontuberculous mycobacteria (NTM) are easily misdiagnosed as multidrug-resistant tuberculosis (MDR-TB), and treatment drugs are very limited. The main objective of our study was to evaluate the minimal inhibitory concentration (MIC) in vitro of bedaquiline (BDQ), clofazimine (CFZ), linezolid (LZD), delamanid (DLM), and pretomanid (PA-824) for treatment of M. abscessus and M. intracellulare. Furthermore, we determined whether MAB_1448, MAB_4384, MAB_2299c, MAB_1483, MAB_0540, rplD, rplC, and rrl were related to drug resistance to provide an experimental basis for the use of these five drugs in the treatment of NTM.

METHODS: We identified sample characteristics of epidemics in 550 patients with suspected NTM infection in Nanjing from 2019 to 2021 using the PCR-reverse spot hybrid method. Furthermore, we evaluated the MIC of BDQ, CFZ, DLM, LZD, and PA-824 against 155 clinical isolates of NTM using the microbroth dilution method. The resistant isolates were sequenced using Sanger sequencing.
RESULTS: The top three dominant species of NTM distributed in Nanjing were M. intracellulare, M. avium, and M. abscessus. Notably, the proportion of M. abscessus infections increased. The proportion of M. abscessus increased from 12% in 2019 to 18% in 2021. Demographic analysis showed that female infection rates were substantialy greater than male for M. abscessus (P=0.017, <0.05). Our results demonstrate that NTM are highly sensitive to bedaquiline and clofazimine in vitro. However, delamanid and pretomanid had little effect on M. abscessus and M. intracellulare. In addition, we found 30-41 nucleotide deletion mutations and some novel point mutations in the MAB_0540 gene of M. abscessus that are resistant to clofazimine.
CONCLUSION: Bedaquiline, clofazimine, and linezolid were more successful in vitro treatments against M. abscessus and M. intracellulare. The MAB_0540 mutation may be associated with resistance of M. abscessus to clofazimine.

DOI: 10.2147/IDR.S408986
PMCID: PMC10171220
PMID: 37180636

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

43. **Genetic Characterization Conferred Co-Resistance to Isoniazid and Ethionamide in Mycobacterium tuberculosis Isolates from Southern Xinjiang, China.**

Infect Drug Resist. 2023 May 19;16:3117-3135. doi: 10.2147/IDR.S407525. eCollection 2023.

Cao B(#)(1)(2), Mijiti X(#)(3), Deng LL(2)(4), Wang Q(3), Yu JJ(1)(2), Anwaierjiang A(5), Qian C(2)(6), Li M(2), Fang DA(2)(6), Jiang Y(2), Zhao LL(2), Zhao X(2), Wan K(2), Liu H(2), Li G(2), Yuan X(1).

BACKGROUND: Ethionamide (ETH), a structural analogue of isoniazid (INH), is used for treating multidrug-resistant tuberculosis (MDR-TB). Due to the common target InhA, INH and ETH showed cross-resistance in M. tuberculosis. This study aimed to explore the INH and ETH resistant profiles and genetic mutations conferring independent INH- or ETH-resistance and INH-ETH cross-resistance in M.

tuberculosis circulating in south of Xinjiang, China.
METHODS: From Sep 2017 to Dec 2018, 312 isolates were included using drug susceptibility testing (DST), spoligotyping, and whole genome sequencing (WGS) to analyze the resistance characteristics for INH and/or ETH.
RESULTS: Among the 312 isolates, 185 (58.3%) and 127 (40.7%) belonged to the Beijing family and non-Beijing family, respectively; 90 (28.9%) were INH-resistant (INHR) with mutation rates of 74.4% in katG, 13.3% in inhA and its promoter, 11.1% in ahpC and its upstream region, 2.2% in ndh, 0.0% in mshA, whilst 34 (10.9%) were ETH-resistant (ETHR) with mutation rates of 38.2% in ethA, 26.2% in inhA and its promoter, and 5.9% in ndh, 0.0% in ethR or mshA; and 25 (8.0%) were INH-ETH co-resistant (INHRETHR) with mutation rates of 40.0% in inhA and its promoter, and 8% in ndh. katG mutants tended to display high-level resistant to INH; and more inhA and its promoter mutants showed low-level of INH and ETH resistance. The optimal gene combinations by WGS for the prediction of INHR, ETHR, and INHRETHR were, respectively, katG+inhA and its promoter (sensitivity: 81.11%, specificity: 90.54%), ethA+inhA and its promoter+ndh (sensitivity: 61.76%, specificity: 76.62%), and inhA and its promoter+ndh (sensitivity: 48.00%, specificity: 97.65%).
CONCLUSION: This study revealed the high diversity of genetic mutations conferring INH and/or ETH resistance among M. tuberculosis isolates, which would facilitate the study on INHR and/or ETHR mechanisms and provide clues for choosing ETH for MDR treatment and molecular DST methods in south of Xinjiang, China.

DOI: 10.2147/IDR.S407525
PMCID: PMC10204763
PMID: 37228658

Conflict of interest statement: We have no conflicts of interest to declare.

44. **Baicalein Suppresses NLRP3 and AIM2 Inflammasome-Mediated Pyroptosis in Macrophages Infected by Mycobacterium tuberculosis via Induced Autophagy.**

Microbiol Spectr. 2023 May 1:e0471122. doi: 10.1128/spectrum.04711-22. Online ahead of print.

Ning B(1), Shen J(1), Liu F(1), Zhang H(1), Jiang X(1).

Mycobacterium tuberculosis (Mtb) continues to pose a significant threat to global health because it causes granulomas and systemic inflammatory responses during active tuberculosis (TB). Mtb can induce macrophage pyroptosis, which

results in the release of IL-1β and causes tissue damage, thereby promoting its spread. In the absence of anti-TB drugs, host-directed therapy (HDT) has been demonstrated to be an effective strategy against TB. In this study, we used an in vitro Mtb-infected macrophage model to assess the effect of baicalein, derived from Scutellariae radix, on pyroptosis induced in Mtb-infected macrophages. Further, we investigated the molecular mechanisms underlying the actions of baicalein. The results of the study suggest that baicalein inhibits pyroptosis in Mtb-infected macrophages by downregulating the assembly of AIM2 and NLRP3 inflammasome and promoting autophagy. Further research has also shown that the mechanism by which baicalein promotes autophagy may involve the inhibition of the activation of the Akt/mTOR pathway and the inhibition of the AIM2 protein, which affects the levels of CHMP2A protein required to promote autophagy. Thus, our data show that baicalein can inhibit Mtb infection-induced macrophage pyroptosis and has the potential to be a new adjunctive HDT drug. IMPORTANCE Current strategies for treating drug-resistant tuberculosis have limited efficacy and undesirable side effects; hence, research on new treatments, including innovative medications, is required. Host-directed therapy (HDT) has emerged as a viable strategy for modulating host cell responses in order to enhance protective immunity against infections. Baicalein, extracted from Scutellariae radix, was shown to inhibit pyroptosis caused by Mycobacterium tuberculosis-infected macrophages and was associated with autophagy. Our findings reveal that baicalein can be used as an adjunctive treatment for tuberculosis or other inflammatory diseases by regulating immune function and enhancing the antibacterial ability of the host. It also provides a new idea for exploring the anti-inflammatory mechanism of baicalein.

DOI: 10.1128/spectrum.04711-22
PMID: 37125940

45. **Residual respiratory disability after successful treatment of pulmonary tuberculosis: a systematic review and meta-analysis.**

EClinicalMedicine. 2023 May 8;59:101979. doi: 10.1016/j.eclinm.2023.101979. eCollection 2023 May.

Taylor J(1), Bastos ML(1)(2), Lachapelle-Chisholm S(1), Mayo NE(3)(4), Johnston J(5), Menzies D(1)(2)(3).

BACKGROUND: Pulmonary tuberculosis (PTB) can result in long-term health consequences, even after successful treatment. We conducted a systematic review and meta-analysis to estimate the occurrence of respiratory impairment, other disability states, and respiratory complications following successful PTB treatment.

METHODS: We identified studies from January 1, 1960, to December 6, 2022, describing populations of all ages that successfully completed treatment for active PTB and had been assessed for at least one of the following outcomes: occurrence of respiratory impairment, other disability states, or respiratory complications following PTB treatment. Studies were excluded if they reported on participants with self-reported TB, extra-pulmonary TB, inactive TB, latent TB, or if participants had been selected on the basis of having more advanced disease. Study characteristics and outcome-related data were abstracted. Meta-analysis was performed using a random effects model. We adapted the Newcastle Ottawa Scale to evaluate the methodological quality of the included studies. Heterogeneity was assessed using the I2 statistic and prediction intervals. Publication bias was assessed using Doi plots and LFK indices. This study is registered with PROSPERO (CRD42021276327).
FINDINGS: 61 studies with 41,014 participants with PTB were included. In 42 studies reporting post-treatment lung function measurements, 59.1% (I2 = 98.3%) of participants with PTB had abnormal spirometry compared to 5.4% (I2 = 97.4%) of controls. Specifically, 17.8% (I2 = 96.6%) had obstruction, 21.3% (I2 = 95.4%) restriction, and 12.7% (I2 = 93.2%) a mixed pattern. Among 13 studies with 3179 participants with PTB, 72.6% (I2 = 92.8%) of participants with PTB had a Medical Research Council dyspnoea score of 1-2 and 24.7% (I2 = 92.2%) a score of 3-5. Mean 6-min walk distance in 13 studies was 440.5 m (I2 = 99.0%) in all participants (78.9% predicted, I2 = 98.9%) and 403.0 m (I2 = 95.1%) among MDR-TB participants in 3 studies (70.5% predicted, I2 = 97.6%). Four studies reported data on incidence of lung cancer, with an incidence rate ratio of 4.0 (95% CI 2.1-7.6) and incidence rate difference of 2.7 per 1000 person-years (95% CI 1.2-4.2) when compared to controls. Quality assessment indicated overall low-quality evidence in this field, heterogeneity was high for pooled estimates of nearly all outcomes of interest, and publication bias was considered likely for almost all outcomes.
INTERPRETATION: The occurrence of post-PTB respiratory impairment, other disability states, and respiratory complications is high, adding to the potential benefits of disease prevention, and highlighting the need for optimised management after successful treatment.
FUNDING: Canadian Institutes of Health Research Foundation Grant.

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PMCID: PMC10189364
PMID: 37205923

Conflict of interest statement: We declare no competing interests.

46. **Survey to measure the quality of life of patients with tuberculosis in Alexandria, Egypt: a cross-sectional study.**

BMC Health Serv Res. 2023 May 24;23(1):534. doi: 10.1186/s12913-023-09381-z.

Hammouda EA(1), Gobran WF(2), Tawfeek RM(3), Esmail OF(4), Ashmawy R(5), Youssef N(6)(7), Ghazy RM(8).

BACKGROUND: Assessment of quality of life (QoL) in patients with tuberculosis (TB) may improve healthcare providers' understanding of the disease burden. This study aimed to investigate the QoL of patients with TB in Alexandria, Egypt.
METHODS: This cross-sectional study was conducted in chest clinics and main chest hospitals in Alexandria, Egypt. A structured interview questionnaire was used to collect data from participants through face-to-face interviews from November 20, 2021, until the June 30, 2022. We included all adult patients aged 18 years or above during the intensive or continuation phase of treatment. The World Health Organization (WHO) WHOQOL-BREF instrument was used to measure QoL, which includes the physical, psychological, social relationships, and environmental health domains. Using propensity score matching, a group of TB free population was recruited from the same setting and completed the questionnaire.
RESULTS: A total of 180 patients participated in the study: 74.4% were males, 54.4% were married, 60.0% were 18-40 years old, 83.3% lived in urban areas, 31.7% were illiterate, 69.5% reported insufficient income, and 10.0% had multidrug-resistant TB. The TB-free population group had higher QoL scores than the TB patients' group: (65.0 ± 17.5 vs. 42.4 ± 17.8) for the physical domain, (59.2 ± 13.6 vs. 41.9 ± 15.1) for the psychological domain, (61.8 ± 19.9 vs. 50.3 ± 20.6) for the social domain, (56.3 ± 19.3 vs. 44.5 ± 12.8) for the environment domain, (4.0(3.0-4.0) vs. 3.0(2.0-4.0)) for general health, and (4.0(3.0-4.0) vs. 2.0(2.0-3.0)) for the general QoL, $P < 0.0001$. Patients with TB aged 18-30 years had the highest environmental score compared with the other age groups ($P = 0.021$).
CONCLUSIONS: TB had a significant negative impact on QoL, with the physical and psychological domains being the most affected. This finding necessitates strategies to improve QoL of patients with to enhance their compliance to treatment.

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PMCID: PMC10208181
PMID: 37226176 [Indexed for MEDLINE]

Conflict of interest statement: All authors declared no conflict of interest.

47. **Hepatitis C care cascade among patients with and without tuberculosis: Nationwide observational cohort study in the country of Georgia, 2015-2020.**

PLoS Med. 2023 May 4;20(5):e1004121. doi: 10.1371/journal.pmed.1004121. eCollection 2023 May.

Baliashvili D(1), Blumberg HM(1)(2)(3), Gandhi NR(1)(2)(3), Averhoff F(4), Benkeser D(5), Shadaker S(6), Gvinjilia L(7), Turdziladze A(8), Tukvadze N(9), Chincharauli M(9), Butsashvili M(10), Sharvadze L(11)(12), Tsertsvadze T(13), Zarkua J(14), Kempker RR(3).

BACKGROUND: The Eastern European country of Georgia initiated a nationwide hepatitis C virus (HCV) elimination program in 2015 to address a high burden of infection. Screening for HCV infection through antibody testing was integrated into multiple existing programs, including the National Tuberculosis Program (NTP). We sought to compare the hepatitis C care cascade among patients with and without tuberculosis (TB) diagnosis in Georgia between 2015 and 2019 and to identify factors associated with loss to follow-up (LTFU) in hepatitis C care among patients with TB.
METHODS AND FINDINGS: Using national ID numbers, we merged databases of the HCV elimination program, NTP, and national death registry from January 1, 2015 to September 30, 2020. The study population included 11,985 adults (aged ≥18 years) diagnosed with active TB from January 1, 2015 through December 31, 2019, and 1,849,820 adults tested for HCV antibodies between January 1, 2015 and September 30, 2020, who were not diagnosed with TB during that time. We estimated the proportion of patients with and without TB who were LTFU at each step of the HCV care cascade and explored temporal changes. Among 11,985 patients with active TB, 9,065 (76%) patients without prior hepatitis C treatment were tested for HCV antibodies, of which 1,665 (18%) had a positive result; LTFU from hepatitis C care was common, with 316 of 1,557 (20%) patients with a positive antibody test not undergoing viremia testing and 443 of 1,025 (43%) patients with viremia not starting treatment for hepatitis C. Overall, among persons with confirmed viremic HCV infection, due to LTFU at various stages of the care cascade only 28% of patients with TB had a documented cure from HCV infection, compared to 55% among patients without TB. LTFU after positive antibody testing substantially decreased in the last 3 years, from 32% among patients diagnosed with TB in 2017 to 12% among those diagnosed in 2019. After a positive HCV antibody test, patients without TB had viremia testing sooner than patients with TB (hazards ratio [HR] = 1.46, 95% confidence intervals [CI] [1.39, 1.54], $p < 0.001$). After a positive viremia test, patients without TB started hepatitis C treatment sooner than patients with TB (HR = 2.05, 95% CI [1.87, 2.25], $p < 0.001$). In the risk factor analysis adjusted for age, sex, and case definition (new versus previously treated), multidrug-resistant (MDR) TB was associated

with an increased risk of LTFU after a positive HCV antibody test (adjusted risk ratio [aRR] = 1.41, 95% CI [1.12, 1.76], p = 0.003). The main limitation of this study was that due to the reliance on existing electronic databases, we were unable to account for the impact of all confounding factors in some of the analyses.
CONCLUSIONS: LTFU from hepatitis C care after a positive antibody or viremia test was high and more common among patients with TB than in those without TB. Better integration of TB and hepatitis C care systems can potentially reduce LTFU and improve patient outcomes both in Georgia and other countries that are initiating or scaling up their nationwide hepatitis C control efforts and striving to provide personalized TB treatment.

DOI: 10.1371/journal.pmed.1004121
PMCID: PMC10194957
PMID: 37141386 [Indexed for MEDLINE]

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

PubMed Non-Open Access Articles

48. Pretomanid-resistant tuberculosis.

J Infect. 2023 May;86(5):520-524. doi: 10.1016/j.jinf.2023.01.039. Epub 2023 Feb 2.

Koehler N(1), Andres S(2), Merker M(3), Dreyer V(4), John A(5), Kuhns M(2), Krieger D(6), Choong E(7), Verougstraete N(8), Zur Wiesch PA(9), Wicha SG(10), König C(11), Kalsdorf B(1), Sanchez Carballo PM(1), Schaub D(1), Werngren J(12), Schön T(13), Peloquin CA(14), Schönfeld N(6), Verstraete AG(15), Decosterd LA(7), Aarnoutse R(16), Niemann S(17), Maurer FP(18), Lange C(19).

DOI: 10.1016/j.jinf.2023.01.039
PMID: 36738862 [Indexed for MEDLINE]

Conflict of interest statement: Declaration of Competing Interest C.K. received personal fees from INFECTOPHARM outside the scope of this work; C.K. received speakers honoraria from GILEAD and SHIONOGI outside the scope of this work; B.K. received personal fees from INSMED outside the scope of this work; S.N. received

grants from German Center for Infection Research, Excellence Cluster Precision Medicine in Chronic Inflammation EXC 2167, and Leibniz Science Campus Evolutionary Medicine of the LUNG (EvoLUNG), during the conduct of the study; S.N. received consultation fees from ILLUMINA outside the scope of this work; C.L. received consulting fees from INSMED outside the scope of this work; C.L. received speakers honoraria from INSMED, GILEAD, and JANSSEN outside the scope of this work; C.L. is a participant on Data Safety Boards of Medicines sans Frontiers outside the scope of this work; all other authors have nothing to disclose.

49. Relative cost of multidrug-resistant TB medicines in Europe.

Int J Tuberc Lung Dis. 2023 May 1;27(5):341-344. doi: 10.5588/ijtld.23.0026.

Günther G(1), Guglielmetti L(2), Leu C(3), van Leth F(4), Lange C(5).

DOI: 10.5588/ijtld.23.0026
PMID: 37143231 [Indexed for MEDLINE]

50. Amorphous Drug Nanoparticles for Inhalation Therapy of Multidrug-Resistant Tuberculosis.

ACS Nano. 2023 May 23;17(10):9478-9486. doi: 10.1021/acsnano.3c01664. Epub 2023 May 9.

Rudolph D(1), Redinger N(2)(3), Schwarz K(4), Li F(5), Hädrich G(5), Cohrs M(6), Dailey LA(5), Schaible UE(2)(3)(7), Feldmann C(1).

Tuberculosis (TB) is one of the most prevalent infectious diseases. The global TB situation is further complicated by increasing patient numbers infected with Mycobacterium tuberculosis (M.tb.) strains resistant to either one or two of the first-line therapeutics, promoted by insufficient treatment length and/or drug levels due to adverse reactions and reduced patient compliance. An intriguing approach to improve anti-TB therapy relates to nanocarrier-based drug-delivery systems, which enhance local drug concentrations at infection sites without systemic toxicity. Recently developed anti-TB antibiotics, however, are lipophilic and difficult to transport in aqueous systems. Here, the very lipophilic TB-antibiotics bedaquiline (BDQ) and BTZ (1,3-benzothiazin-4-one 043) are prepared as high-dose, amorphous nanoparticles via a solvent-antisolvent technique. The nanoparticles exhibit mean diameters of 60 ± 13 nm (BDQ) and 62 ± 44 nm (BTZ) and have an extraordinarily high drug load with 69% BDQ and >99% BTZ of total nanoparticle mass plus a certain amount of surfactant (31% for BDQ, <1% for BTZ) to make the lipophilic drugs water-dispersible. Suspensions with high drug load (4.1 mg/mL BDQ, 4.2 mg/mL BTZ) are stable for several weeks. In vitro

and in vivo studies employing M.tb.-infected macrophages and susceptible C3HeB/FeJ mice show promising activity, which outperforms conventional BDQ/BTZ solutions (in DMF or DMSO) with an up to 50% higher efficacy upon pulmonary delivery. In vitro, the BDQ/BTZ nanoparticles demonstrate their ability to cross the different biological barriers and to reach the site of the intracellular mycobacteria. In vivo, high amounts of the BDQ/BTZ nanoparticles are found in the lung and specifically inside granulomas, whereas only low BDQ/BTZ-nanoparticle levels are observed in spleen or liver. Thus, pulmonary delivered BDQ/BTZ nanoparticles are promising formulations to improve antituberculosis treatment.

DOI: 10.1021/acsnano.3c01664
PMCID: PMC10211367
PMID: 37160267 [Indexed for MEDLINE]

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

51. Drug resistant tuberculosis in Italy through a global health lens.

New Microbiol. 2023 May;46(2):120-132.

Fama F(1)(2)(3), Genovese C(1)(2)(3), Raviglione M(3), Gori A(1)(2)(3).

Drug-resistant tuberculosis (DR-TB) is a major global health challenge. In 2021, about one third of DR-TB patients worldwide were enrolled in treatment. In order to reach the targets set during by the 2018 UN General Assembly (UNGA) Political Declaration on Tuberculosis, a global effort must be made by both high- and low-incidence countries. Data concerning high-incidence countries are vast in the literature, but insufficient political attention has been paid in low-incidence countries to face this infectious threat. This review aims at providing an overview of DR-TB focused on different facets of DR-TB management. First, global and Italian data on the main at-risk populations for TB and DR-TB were gathered, together with the latest studies on the correlation between TB risk factors and the onset of drug resistance. Second, this review provides an analysis of obsolete Italian guidelines on the diagnosis and management of TB and DR-TB, highlighting the challenges that our country is currently facing to properly implement the latest international recommendations. Finally, some key suggestions are provided to design public health (PH) policies that can effectively tackle the DR-TB issue from a "global health" perspective.

PMID: 37247232

52. A systematic review of the costs of diagnosis for multidrug-resistant/extensively drug-resistant TB in different settings.

Int J Tuberc Lung Dis. 2023 May 1;27(5):348-356. doi: 10.5588/ijtld.22.0657.

Saderi L(1), Cabibbe AM(2), Puci M(1), Di Lorenzo B(1), Centis R(3), Pontali E(4), van den Boom M(5), Chakaya JM(6), D Ambrosio L(7), Denholm JT(8), Ferrara G(9), Silva DR(10), Solovic I(11), Spanevello A(12), Visca D(12), Sotgiu G(1), Migliori GB(3).

BACKGROUND: We performed an analysis of the cost and relative merits of different strategies for the diagnosis of multidrug-resistant/extensively drug-resistant TB (MDR/XDR-TB) in different settings.METHODS: We systematically reviewed the published evidence on cost/cost-effectiveness of rapid MDR/pre-XDR-TB and other methods for XDR-TB testing up to September 2022. PRISMA guidelines were followed. Collected data were analysed using Stata v17 software. Cost data were reported in USD ($) and summarised by mean, standard deviation, and range. Country income level was defined according to the World Bank country classification. Three simplified scenarios were also used to explore testing implications, based on low, intermediate and high TB incidence.RESULTS: Of 157 records, 25 studies were included with 24 reporting the cost of Xpert/RIF and two that evaluated the implementation of the MTBDRplus test. The total rapid test cost ranged from $12.41-$218, including $1.13-$74.60 for reagents/consumables and $0.40-$14.34 for equipment.CONCLUSION: The cost of MDR/XDR-TB diagnostics is lower in low resource settings. However, the cost-effective implementation of MDR/XDR-TB diagnostic algorithms requires careful consideration of local resources to avoid missed identification and the use of inappropriate regimen.

DOI: 10.5588/ijtld.22.0657
PMID: 37143228 [Indexed for MEDLINE]

53. One-year incidence of tuberculosis infection and disease among household contacts of rifampin- and multi-drug resistant tuberculosis.

Clin Infect Dis. 2023 May 25:ciad301. doi: 10.1093/cid/ciad301. Online ahead of print.

Krishnan S(1), Wu X(2), Kim S(3), McIntire K(1), Naini L(4), Hughes MD(2), Dawson R(5), Mave V(1)(6), Gaikwad S(6), Sanchez J(7), Mendoza-Ticona A(8), Gonzales P(7), Comins K(8), Shenje J(9), Nerette Fontain S(10), Omozoarhe A(11), Mohapi L(12), Lalloo UG(13), Garcia Ferreira AC(14), Mugah C(15), Harrington M(16), Shah NS(17), Hesseling AC(18), Churchyard G(19)(20)(21), Swindells S(22), Gupta A(1)(6); AIDS Clinical Trials Group (ACTG) A5300/International Maternal

Pediatric Adolescent AIDS Clinical Trials (IMPAACT) I2003 Protecting Households on Exposure to Newly Diagnosed Index Multidrug-resistant Tuberculosis Patients (PHOENIx) Feasibility Study Team.

Collaborators: Chaisson RE, Johnson D, Siberry GK, Smith E, Demers AM, Kanade S, Nicotera J, Anthony P, Lane C, Kadam UA, Ssenyonga R, Shahkolahi A, Jones L, Heckman B, Manzella A.

BACKGROUND: Tuberculosis infection (TBI) and tuberculosis disease (TBD) incidence remains poorly described following household contact (HHC) rifampin-/multidrug-resistant tuberculosis exposure. We sought to characterize TBI and TBD incidence at one-year in HHCs and to evaluate tuberculosis preventive therapy (TPT) use in high-risk groups.
METHODS: We previously conducted a cross-sectional study of HHCs of rifampin-/multidrug-resistant tuberculosis in 8 high-burden countries and re-assessed TBI (interferon-gamma release assay, HHCs ≥5 years) and TBD (HHCs all ages) at one-year. Incidence was estimated across age and risk groups (age <5 years; age ≥5 years, HIV-positive; age ≥5 years, HIV-negative/unknown, baseline TBI positive) by logistic or log-binomial regression fitted using generalized estimating equations.
RESULTS: Of 1016 HHCs, 850 (83.7%) from 247 households were assessed (median: 51.4 weeks). Among 242 HHCs, 52 tested interferon-gamma release assay-positive, yielding a one-year 21.6% (95% CI 16.7-27.4) TBI cumulative incidence. Sixteen of 742 HHCs developed confirmed (n=5), probable (n=3) or possible (n=8) TBD, yielding a 2.3% (95% CI 1.4-3.8) one-year cumulative incidence (1.1% [95% CI 0.5-2.2] for confirmed/probable TBD). TBD relative risk was 11.5 (95% CI 1.7-78.7), 10.4 (95% CI 2.4-45.6), and 2.9 (95% CI 0.5-17.8) fold higher in age <5 years, HIV+, and baseline TBI high-risk groups, respectively, versus not high-risk group (p=0.0015). By one-year, 4% (21 of 553) high-risk HHCs received TPT.
CONCLUSIONS: TBI and TBD incidence continued through one-year in rifampin-/multidrug-resistant tuberculosis HHCs. Low TPT coverage emphasizes need for evidence-based prevention and scale-up, particularly among high-risk groups.

DOI: 10.1093/cid/ciad301
PMID: 37227925

54. Shorter regimens improved treatment outcomes of multidrug-resistant tuberculosis patients in Tanzania in 2018 cohort.

Trop Med Int Health. 2023 May;28(5):357-366. doi: 10.1111/tmi.13867. Epub 2023 Mar 20.

Mleoh L(1), Mziray SR(2)(3), Tsere D(2), Koppelaar I(4), Mulder C(4)(5), Lyakurwa D(6).

OBJECTIVE: In 2018, shorter treatment regimens (STR) for people with drug-resistant tuberculosis (DR-TB) were introduced in Tanzania and included kanamycin, high-dose moxifloxacin, prothionamide, high-dose isoniazid, clofazimine, ethambutol and pyrazinamide. We describe treatment outcomes of people diagnosed with DR-TB in a cohort initiating treatment in 2018 in Tanzania.
METHODS: This was a retrospective cohort study conducted at the National Centre of Excellence and decentralised DR-TB treatment sites for the 2018 cohort followed from January 2018 to August 2020. We reviewed data from the National Tuberculosis and Leprosy Program DR-TB database to assess clinical and demographic information. The association between different DR-TB regimens and treatment outcome was assessed using logistic regression analysis. Treatment outcomes were described as treatment complete, cure, death, failure or lost to follow-up. A successful treatment outcome was assigned when the patient achieved treatment completion or cure.
RESULTS: A total of 449 people were diagnosed with DR-TB of whom 382 had final treatment outcomes: 268 (70%) cured; 36 (9%) treatment completed; 16 (4%) lost to follow-up; 62 (16%) died. There was no treatment failure. The treatment success rate was 79% (304 patients). The 2018 DR-TB treatment cohort was initiated on the following regimens: 140 (46%) received STR, 90 (30%) received the standard longer regimen (SLR), 74 (24%) received a new drug regimen. Normal nutritional status at baseline [adjusted odds ratio (aOR) = 6.57, 95% CI (3.33-12.94), $p < 0.001$] and the STR [aOR = 2.67, 95% CI (1.38-5.18), $p = 0.004$] were independently associated with successful DR-TB treatment outcome.
CONCLUSION: The majority of DR-TB patients on STR in Tanzania achieved a better treatment outcome than on SLR. The acceptance and implementation of STR at decentralised sites promises greater treatment success. Assessing and improving nutritional status at baseline and introducing new shorter DR-TB treatment regimens may strengthen favourable treatment outcomes.

DOI: 10.1111/tmi.13867
PMID: 36864011 [Indexed for MEDLINE]

55. Role of non-coding rnas in tuberculosis and their potential for clinical applications.

J Appl Microbiol. 2023 May 17:lxad104. doi: 10.1093/jambio/lxad104. Online ahead of print.

Jumat MI(1), Sarmiento ME(2), Acosta A(2), Chin KL(1).

Tuberculosis (TB), caused by Mycobacterium tuberculosis (Mtb), remains the leading cause of mortality due to infectious diseases, only surpassed in 2020 by COVID-19. Despite the development in diagnostics, therapeutics, and evaluation of new vaccines for TB, this infectious disease remains uncontrollable due to the emergence of multi-drug resistant (MDR) and extremely-drug resistant (XDR) TB, among other factors. The development in transcriptomics (RNomics) has enabled the study of gene expression in TB. It is considered that non-coding RNAs (ncRNAs) from host [microRNAs (miRNAs)] and Mtb [small RNAs (sRNAs)] are important elements in TB pathogenesis, immune resistance, and susceptibility. Many studies have shown the importance of host miRNAs in regulating immune response against Mtb via in vitro and in vivo mice models. The bacterial sRNAs play a major role in survival, adaptation, and virulence. Here, we review the characterization and function of host and bacteria ncRNAs in TB and their potential use in clinical applications as diagnostic, prognostic, and therapeutic biomarkers.

DOI: 10.1093/jambio/lxad104
PMID: 37197901

56. Population Pharmacokinetics and Dose Evaluation of Cycloserine among Patients with Multidrug-Resistant Tuberculosis under Standardized Treatment Regimens.

Antimicrob Agents Chemother. 2023 May 17;67(5):e0170022. doi: 10.1128/aac.01700-22. Epub 2023 Apr 25.

Zhu Y(#)(1), Zhu L(#)(2), Davies Forsman L(#)(3)(4), Paues J(5)(6), Werngren J(7), Niward K(5)(6), Schön T(5)(6)(8), Bruchfeld J(3)(4), Xiong H(#)(1), Alffenaar JW(#)(9)(10)(11), Hu Y(#)(1).

Although cycloserine is a recommended drug for the treatment of multidrug-resistant tuberculosis (MDR-TB) according to World Health Organization (WHO), few studies have reported on pharmacokinetics (PK) and/or pharmacodynamics (PD) data of cycloserine in patients with standardized MDR-TB treatment. This study aimed to estimate the population PK parameters for cycloserine and to identify clinically relevant PK/PD thresholds, as well as to

evaluate the current recommended dosage. Data from a large cohort with full PK curves was used to develop a population PK model. This model was used to estimate drug exposure in patients with MDR-TB from a multicentre prospective study in China. The classification and regression tree was used to identify the clinically relevant PK/PD thresholds. Probability of target attainment was analyzed to evaluate the currently recommended dosing strategy. Cycloserine was best described by a two-compartment disposition model. A percentage of time concentration above MICs (T>MIC) of 30% and a ratio of area under drug concentration-time curve (AUC0-24h) over MIC of 36 were the valid predictors for 6-month sputum culture conversion and final treatment outcome. Simulations showed that with WHO-recommended doses (500 mg and 750 mg for patients weighing <45 kg and ≥45 kg), the probability of target attainment exceeded 90% at MIC ≤16 mg/L in MGIT for both T>MIC of 30% and AUC0-24h/MIC of 36. New clinically relevant PK/PD thresholds for cycloserine were identified in patients with standardized MDR-TB treatment. WHO-recommended doses were considered adequate for the MGIT MIC distribution in our cohort of Chinese patients with MDR-TB.

DOI: 10.1128/aac.01700-22
PMCID: PMC10190270
PMID: 37097151 [Indexed for MEDLINE]

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

57. Current therapeutic delivery approaches using nanocarriers for the treatment of tuberculosis disease.

Int J Pharm. 2023 Jun 10;640:123018. doi: 10.1016/j.ijpharm.2023.123018. Epub 2023 May 4.

Biswas B(1), Misra TK(2), Ray D(3), Majumder T(3), Bandyopadhyay TK(1), Bhowmick TK(4).

Tuberculosis is a major health issue globally and a leading cause of death due to the infective microorganism Mycobacterium tuberculosis. Treatment of drug resistance tuberculosis requires longer treatment with multiple daily doses of drugs. Unfortunately, these drugs are often associated with poor patient compliance. In this situation, a need has been felt for the less toxic, shorter, and more effective treatment of the infected tuberculosis patients. Current research to develop novel anti-tubercular drugs shows hope for better management of the disease. Research on drug targeting and precise delivery of the old anti-tubercular drugs with the help of nanotechnology is promising for effective treatment. This review has discussed the status currently available treatments for tuberculosis patients infected with Mycobacterium alone or in comorbid conditions like diabetes, HIV and cancer. This review also highlighted the

challenges in the current treatment and research on the novel anti-tubercular drugs to prevent multi-drug-resistant tuberculosis. It presents the research highlights on the targeted delivery of anti-tubercular drugs using different nanocarriers for preventing multi-drug resistant tuberculosis. Report has shown the importance and development of the research on nanocarriers mediated anti-tubercular delivery of the drugs to overcome the current challenges in tuberculosis treatment.

DOI: 10.1016/j.ijpharm.2023.123018
PMID: 37149113 [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.

58. Updated considerations in the diagnosis and management of tuberculosis infection and disease: integrating the latest evidence-based strategies.

Expert Rev Anti Infect Ther. 2023 Jun;21(6):595-616. doi: 10.1080/14787210.2023.2207820. Epub 2023 May 8.

Graciaa DS(1), Schechter MC(1), Fetalvero KB(2)(3), Cranmer LM(4)(5)(6), Kempker RR(1), Castro KG(1)(5)(7).

INTRODUCTION: Tuberculosis (TB) is a leading infectious cause of global morbidity and mortality, affecting nearly a quarter of the human population and accounting for over 10 million deaths each year. Over the past several decades, TB incidence and mortality have gradually declined, but 2021 marked a threatening reversal of this trend highlighting the importance of accurate diagnosis and effective treatment of all forms of TB.
AREAS COVERED: This review summarizes advances in TB diagnostics, addresses the treatment of people with TB infection and TB disease including recent evidence for treatment regimens for drug-susceptible and drug-resistant TB, and draws attention to special considerations in children and during pregnancy.
EXPERT OPINION: Improvements in diagnosis and management of TB have expanded the available options for TB control. Molecular testing has enhanced the detection of TB disease, but better diagnostics are still needed, particularly for certain populations such as children. Novel treatment regimens have shortened treatment and improved outcomes for people with TB. However, important questions remain regarding the optimal management of TB. Work must continue to ensure the potential of the latest developments is realized for all people affected by TB.

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PMCID: PMC10227769
PMID: 37128947 [Indexed for MEDLINE]

Conflict of interest statement: Declaration of interest KG Castro has an Intergovernmental Personnel Act (IPA) award to serve as Senior TB Scientific Advisor, Office of Infectious Disease, Bureau for Global Health, U.S. Agency for International Development. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

59. Comparative safety of bedaquiline and delamanid in patients with multidrug resistant tuberculosis: A nationwide retrospective cohort study.

J Microbiol Immunol Infect. 2023 May 2:S1684-1182(23)00087-7. doi: 10.1016/j.jmii.2023.04.009. Online ahead of print.

Kim JH(1), Lee H(2), Oh IS(2), Jeong HE(2), Bea S(1), Jang SH(3), Son H(4), Shin JY(5).

BACKGROUND/PURPOSE(S): Bedaquiline and delamanid were recently approved for multidrug resistant tuberculosis (MDR-TB). Bedaquiline carries a black box warning of increased risk of death compared to the placebo arm, and there is a need to establish the risks of QT prolongation and hepatotoxicity for bedaquiline and delamanid.
METHODS: We retrospectively analyzed data of MDR-TB patients retrieved from the South Korea national health insurance system database (2014-2020) to assess the risks of all-cause death, long QT-related cardiac event, and acute liver injury associated with bedaquiline or delamanid, compared with conventional regimen. Cox proportional hazards models were used to estimate hazard ratios (HR) with 95% confidence intervals (CI). Stabilized inverse probability of treatment weighting based on propensity score was used to balance characteristics between the treatment groups.
RESULTS: Of 1998 patients, 315 (15.8%) and 292 (14.6%) received bedaquiline and delamanid, respectively. Compared with conventional regimen, bedaquiline and delamanid did not increase risk of all-cause death at 24-month (HR 0.73 [95% CI, 0.42-1.27] and 0.89 [0.50-1.60], respectively). Bedaquiline-containing regimen increased risk of acute liver injury (1.76 [1.31-2.36]), while delamanid-containing regimen increased risk of long QT-related cardiac events (2.38 [1.05-3.57]) within 6 months of treatment.
CONCLUSION: This study adds to the emerging evidence refuting the higher mortality rate observed in the bedaquiline trial population. Association between

bedaquiline and acute liver injury needs careful interpretation considering for other background hepatotoxic anti-TB drugs. Our finding on delamanid and long QT-related cardiac events suggest careful risk-benefit assessment in patients with pre-existing cardiovascular disease.

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PMID: 37202241

Conflict of interest statement: Declaration of competing interest J-YS received grants from the Ministry of Food and Drug Safety, Ministry of Health and Welfare, National Research Foundation of Korea, and pharmaceutical companies including Daiichi Sankyo, GSK and Pfizer outside the submitted work.

60. Multitargeting: An Alternative Approach to Tackling Multidrug Resistance Issues in Tuberculosis.

Curr Drug Targets. 2023 May 5. doi: 10.2174/1389450124666230505145335. Online ahead of print.

Hazra S(1), Hazarika R(2), Patra S(1).

BACKGROUND: The prevalence of drug-resistant organisms has steadily increased over the past few decades worldwide. Especially in tuberculosis (TB) disease, the problems of co-morbidity and the rapid emergence of multidrug resistance have necessitated the development of multitarget-based therapeutic regimens. Several multitargeting compounds against Mycobacterium tuberculosis (Mtb) have been studied through novel in silico tools but these have rendered reduced efficacy in clinical trials. The authors have focussed on many exotic targets belonging to crucial Mtb survival pathways whose molecular structures and functions are underexplored. Likewise, insights into the hidden possibilities of promiscuous compounds from natural products or repurposed drugs to inhibit other cellular proteins apart from their validated targets are also depicted in this review. In addition to the existing line of drugs currently recommended for multidrug-resistant TB, newer host-directed therapies could also be fruitful. Furthermore, several challenges, including safety/efficacy ratios of multitarget compounds highlighted here, can also be circumnavigated by researchers to design "smart drugs" for improved tuberculosis therapeutics.
CONCLUSION: A holistic approach towards alleviating the existing drawbacks of drug discovery in drug-resistant TB has been outlined. Finally, considering the current needs, the authors have put forward an overall summary of possible trends in multitargeting that are significant for futuristic therapeutic solutions.

DOI: 10.2174/1389450124666230505145335
PMID: 37151074

61. Efficacy and safety of video-assisted thoracoscopic surgery for pulmonary TB.

Int J Tuberc Lung Dis. 2023 May 1;27(5):387-394. doi: 10.5588/ijtld.22.0671.

Tang J(1), Tang Z(1), Feng C(1), Tang Q(2).

OBJECTIVE: Compared with thoracotomy, video-assisted thoracoscopic surgery (VATS) has the advantage of post-operative recovery for patients undergoing surgery. However, studies comparing the efficacy of VATS with conventional traditional thoracotomy for treating patients with pulmonary TB (PTB) are inconsistent.METHODS: Five electronic databases were used to search studies on VATS and conventional thoracotomy for PTB up to 15 March 2022. Standardised mean differences (SMDs) and odds ratios (ORs) were calculated for comparison.RESULTS: A total of 14 were included. Compared with traditional thoracotomy, patients with drug-resistant TB treated using VATS had shorter operative time, less intra-operative bleeding, faster post-operative recovery and fewer post-operative complications (operation time: SMD -0.87, 95% CI -1.29 to -0.45; blood loss: SMD -1.31, 95% CI -1.71 to -0.92; duration of hospital stay: SMD -1.68, 95% CI -2.46 to -0.90; catheterisation time: SMD -1.56, 95% CI -2.39 to -0.73; post-operative complication: OR 0.40, 95% CI 0.27 to 0.60).CONCLUSION: Compared with conventional thoracotomy, VATS for patients with multidrug-resistant PTB undergoing lobectomy and wedge resection has the advantages of minor bleeding, shorter operative time, shorter hospital stay and post-operative pleural cavity drainage duration, and fewer post-operative complications, which can accelerate the post-operative recovery of patients.

DOI: 10.5588/ijtld.22.0671
PMID: 37143223 [Indexed for MEDLINE]

62. Global status of phenotypic pyrazinamide resistance in Mycobacterium tuberculosis clinical isolates: an updated systematic review and meta-analysis.

J Chemother. 2023 May 21:1-13. doi: 10.1080/1120009X.2023.2214473. Online ahead of print.

Wang Z(1), Tang Z(1), Heidari H(2), Molaeipour L(3), Ghanavati R(4), Kazemian H(5), Koohsar F(6), Kouhsari E(6)(7).

Pyrazinamide (PZA) is an essential first-line tuberculosis drug for its unique mechanism of action active against multidrug-resistant-TB (MDR-TB). Thus, the aim of updated meta-analysis was to estimate the PZA weighted pooled resistance (WPR) rate in M. tuberculosis isolates based on publication date and WHO regions. We systematically searched the related reports in PubMed, Scopus, and Embase (from January 2015 to July 2022). Statistical analyses were performed using STATA software. The 115 final reports in the analysis investigated phenotypic PZA resistance data. The WPR of PZA was 57% (95% CI 48-65%) in MDR-TB cases. According to the WHO regions, the higher WPRs of PZA were reported in the Western Pacific (32%; 95% CI 18-46%), South East Asian region (37%; 95% CI 31-43%), and the Eastern Mediterranean (78%; 95% CI 54-95%) among any-TB patients, high risk of MDR-TB patients, and MDR-TB patients, respectively. A negligible increase in the rate of PZA resistance were showed in MDR-TB cases (55% to 58%). The rate of PZA resistance has been rising in recent years among MDR-TB cases, underlines the essential for both standard and novel drug regimens development.

DOI: 10.1080/1120009X.2023.2214473
PMID: 37211822

63. [Clinical value of the MeltPro MTB assays in detection of drug-resistant tuberculosis in paraffin-embedded tissues].

Zhonghua Bing Li Xue Za Zhi. 2023 May 8;52(5):466-471. doi: 10.3760/cma.j.cn112151-20230103-00004.

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

Che JL(1), Liu ZC(1), Li K(1), Du WL(1), Zhao D(1), Mu J(1), Dong YJ(1), Che NY(1).

Objective: To evaluate the clinical value of the MeltPro MTB assays in the diagnosis of drug-resistant tuberculosis. Methods: A cross-sectional study design was used to retrospectively collect all 4 551 patients with confirmed tuberculosis between January 2018 and December 2019 at Beijing Chest Hospital, Capital Medical University. Phenotypic drug sensitivity test and GeneXpert MTB/RIF (hereafter referred to as "Xpert") assay were used as gold standards to analyze the accuracy of the probe melting curve method. The clinical value of this technique was also evaluated as a complementary method to conventional assays of drug resistance to increase the detective rate of drug-resistant tuberculosis. Results: By taking the phenotypic drug susceptibility test as the gold standard, the sensitivity of the MeltPro MTB assays to detect resistance to

rifampicin, isoniazid, ethambutol and fluoroquinolone was 14/15, 95.7%(22/23), 2/4 and 8/9,respectively; and the specificity was 92.0%(115/125), 93.2%(109/117), 90.4%(123/136) and 93.9%(123/131),respectively; the overall concordance rate was 92.1%(95%CI:89.6%-94.1%),and the Kappa value of the consistency test was 0.63(95%CI:0.55-0.72).By taking the Xpert test results as the reference, the sensitivity of this technology to the detection of rifampicin resistance was 93.6%(44/47), the specificity was100%(310/310), the concordance rate was 99.2%(95%CI:97.6%-99.7%), and the Kappa value of the consistency test was 0.96(95%CI:0.93-0.99). The MeltPro MTB assays had been used in 4 551 confirmed patients; the proportion of patients who obtained effective drug resistance results increased from 83.3% to 87.8%(P<0.01); and detection rate of rifampicin, isoniazid, ethambutol, fluoroquinolone resistance, multidrug and pre-extensive drug resistance cases were increased by 3.2%, 14.7%, 22.2%, 13.7%, 11.2% and 12.5%, respectively. Conclusion: The MeltPro MTB assays show satisfactory accuracy in the diagnosis of drug-resistant tuberculosis. This molecular pathological test is an effective complementary method in improving test positivity of drug-resistant tuberculosis.

DOI: 10.3760/cma.j.cn112151-20230103-00004
PMID: 37106288 [Indexed for MEDLINE]

64. World Health Organization Guideline on the Management of Tuberculosis in Children: Critical Appraisal, Concerns, and Caution.

Indian J Pediatr. 2023 May 17. doi: 10.1007/s12098-023-04584-y. Online ahead of print.

Kumar K(1), Mathew JL(2).

In September 2022, the World Health Organization (WHO) published a new guideline for the management of tuberculosis (TB) in children and adolescents. It included eight new recommendations. Xpert MTB/RIF Ultra (Xpert Ultra) has been designated as the preferred initial diagnostic test for pulmonary TB and detection of rifampicin resistance. But its place vis-à-vis the previously recommended GeneXpert has not been clarified. Further, the limited diagnostic accuracy of Xpert Ultra in some biological specimens like nasopharyngeal aspirates, and the inability to report the presence or absence of rifampicin resistance in 'trace' reports has not been addressed. The guideline also recommends a shortened 4-mo treatment regimen for non-severe drug-susceptible TB. This is based on a single trial having several methodological issues that limit its applicability and generalizability. Interestingly, the criteria for designating 'non-severe' TB in the trial is based on smear negativity, whereas the new WHO recommendation is to omit smear microscopy altogether. The guideline also recommends an alternative 6-mo intensive regimen for drug-susceptible TB meningitis, which needs more

supportive evidence. The lower age limits for the use of bedaquiline and delamanid have been decreased to less than 6 and 3 y respectively. While this makes it feasible to treat drug resistant TB in children with oral medications, the resource implications need careful consideration. These concerns advocate caution before the WHO guideline recommendations can be universally implemented.

DOI: 10.1007/s12098-023-04584-y
PMID: 37193925

65. Cisatracurium besylate rescues Mycobacterium Tuberculosis-infected macrophages from necroptosis and enhances the bactericidal effect of isoniazid.

Int Immunopharmacol. 2023 May 12;120:110291. doi: 10.1016/j.intimp.2023.110291. Online ahead of print.

Wen Q(1), Zhang J(1), Zhang Z(1), Chen L(1), Liu H(1), Han Z(1), Chen Y(1), Wang K(1), Liu J(1), Sai N(1), Zhou X(1), Zhou C(1), Hu S(1), Ma L(2).

OBJECTIVE: Tuberculosis is the leading killer among the chronic single-source infectious diseases. Mycobacterium tuberculosis can induce necrotic-dominant multiple modes of cell death in macrophages, which accelerates bacterium dissemination and expands tissue injury in host lungs. Mining drugs to counteract Mycobacterium tuberculosis-induced cell death would be beneficial to tuberculosis patients.
METHODS: In this study, the protective drug was screened out from the FDA-approved drug library in Mycobacterium tuberculosis-infected macrophages with CCK-8 assay. The death mode regulated by the drug was identified using transcriptomic sequencing, cytomorphological observation, and in the experimental mouse Mycobacterium tuberculosis-infection model. The functional mechanism was explored using western blot, co-immunoprecipitation, and DARTS assay. The intracellular bacterial survival was detected using colony forming unit assays.
RESULTS: Cisatracurium besylate was identified to be highly protective for the viability of macrophages during Mycobacterium tuberculosis infection via inhibiting necroptosis. Cisatracurium besylate prevented RIPK3 to be associated with the executive molecule MLKL for forming the necroptotic complex, resulting in the inhibition of MLKL phosphorylation and pore formation on cell membrane. However, Cisatracurium besylate did not interfere with the association between RIPK3 with its upstream kinase RIPK1 or ZBP1 but regulated RIPK3 autophosphorylation. Moreover, Cisatracurium besylate significantly inhibited the expansion of intracellular Mycobacterium tuberculosis both in vitro and in vivo, which also displayed a strong auxiliary bacteriostatic effect to support

the therapeutic efficacy of isoniazid and rifampicin, the first-line anti-tubercular drugs.
CONCLUSION: Cisatracurium besylate performs anti-Mycobacterium tuberculosis and anti-necroptotic roles, which potentiates its application to be an adjuvant drug for antituberculosis therapy to assist the battle against drug-resistant tuberculosis.

DOI: 10.1016/j.intimp.2023.110291
PMID: 37182451

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.

66. Nanomotion technology in combination with machine learning: a new approach for a rapid antibiotic susceptibility test for Mycobacterium tuberculosis.

Microbes Infect. 2023 May 17:105151. doi: 10.1016/j.micinf.2023.105151. Online ahead of print.

Vocat A(1), Sturm A(2), Jozwiak G(2), Cathomen G(2), Świątkowski M(2), Buga R(2), Wielgoszewski G(2), Cichocka D(2), Greub G(3), Opota O(4).

Nanomotion technology is a growth-independent approach that can be used to detect and record the vibrations of bacteria attached to microcantilevers. We have developed a nanomotion-based antibiotic susceptibility test (AST) protocol for Mycobacterium tuberculosis (MTB). The protocol was used to predict strain phenotype towards isoniazid (INH) and rifampicin (RIF) using a leave-one-out cross-validation (LOOCV) and machine learning techniques.. This MTB-nanomotion protocol takes 21 hours, including cell suspension preparation, optimized bacterial attachment to functionalized cantilever, and nanomotion recording before and after antibiotic exposure. We applied this protocol to MTB isolates (n=40) and were able to discriminate between susceptible and resistant strains for INH and RIF with a maximum sensitivity of 97.4% and 100%, respectively, and a maximum specificity of 100% for both antibiotics when considering each nanomotion recording to be a distinct experiment. Grouping recordings as triplicates based on source isolate improved sensitivity and specificity to 100% for both antibiotics. Nanomotion technology can potentially reduce time-to-result significantly compared to the days and weeks currently needed for current phenotypic ASTs for MTB. It can further be extended to other anti-TB drugs to help guide more effective TB treatment.

DOI: 10.1016/j.micinf.2023.105151
PMID: 37207717

67. Feasibility and acceptability pilot of video-based direct observed treatment (vDOT) for supporting antitubercular treatment in South India: a cohort study.

BMJ Open. 2023 May 29;13(5):e065878. doi: 10.1136/bmjopen-2022-065878.

Rodrigues R(1)(2)(3), Varghese SS(4), Mahrous M(5), Ananthaneni Kumar A(4), Ahmed MN(4)(6), D'Souza G(7).

OBJECTIVES: The objective of this study was to assess the feasibility and acceptability of video-based anti-tuberculosis (TB) treatment adherence support in patients with TB (PwTB) in South India.
DESIGN: An exploratory cohort.
SETTING: Participants were recruited at the TB treatment centre (direct observed treatment short centre) of a tertiary-level teaching facility in Bangalore, Karnataka, South India.
PARTICIPANTS: The study enrolled 25 PwTB, with replacement. Adult PwTB who were on drug-sensitive treatment regimens were included, while those who had drug resistant TB were excluded from the study.
INTERVENTION: Participants received scheduled adherence reminders and were trained to videorecord themselves swallowing their medication via a mobile application. The application was automated to submit these videos for evaluation. Participants were followed up monthly till treatment completion or withdrawal.
OUTCOME MEASURES: Adherence rate and acceptability of video-based directly observed treatment (vDOT).
RESULTS: The mean±SD age of the participants was 33±14 years, majority were females (16, 64%), residing in urban areas (24,96%), married (17, 68%) and had access to smart phones (23,92%). A total of 3193 person days of follow-up was completed; of the videos submitted within the first 6 months of enrollment (2501), 94% (2354/2501) were considered 'acceptable' and 16 (64%) participants were optimally adherent (ie, ≥80%). Participant videos improved in quality and a higher proportion met acceptability criteria over time. Twenty-one (84%) participants stated that they found the application easy to learn; 13 (52%) preferred vDOT over DOT. Mixed model logistic regression showed that those who are married are more likely have daily adherence to anti-TB treatment.
CONCLUSION: Video-based mobile phone interventions are acceptable to PwTB and the ease of using the application increases with time. To provide

patient-centred care, vDOT is a promising option that can be offered to patients for treatment support and adherence monitoring.

DOI: 10.1136/bmjopen-2022-065878
PMID: 37247959

Conflict of interest statement: Competing interests: None declared.

68. In silico analysis to identify potential antitubercular molecules in Morus alba through virtual screening and molecular dynamics simulations.

J Biomol Struct Dyn. 2023 May 8:1-8. doi: 10.1080/07391102.2023.2209648. Online ahead of print.

Khan M(1)(2), Khan S(3)(2), Alshammary FL(2)(4), Zaidi S(5), Singh V(5)(6), Ahmad I(7), Patel H(7), Gupta VK(8), Haque S(9)(10)(11).

A major obstacle in the treatment of tuberculosis (TB) is to combat the emerging resistant strains of its causing agent i.e. Mycobacterium tuberculosis (MTb). The emergence of multidrug-resistant and extensively drug-resistant -TB strains raise a requirement of new potential anti-tubercular compounds. In this direction, different plant parts of Morus alba were tested against MTb and found to be active with a minimum inhibitory concentration ranging between 125 µg/ml to 31.5 µg/ml. Further to identify the phytochompounds having anti-mycobacterium activity, phytocompounds of the plant were docked against the five MTb proteins (PDB ID: 3HEM, 4OTK, 2QO0, 2AQ1 and 6MNA). Among twenty-two tested phytocompounds, four phytocompounds with effective binding energy (kcal/mol): Petunidin-3-rutinoside (3HEM: -8.2, 4OTK: -6.9, 2QO0: -9.0, 2AQ1: -8.3 and 6MNA:-7.8), Quercetin-3'-glucoside (3HEM:-6.7, 4OTK:-7.6, 2QO0:-7.6, 2AQ1:7.6 and 6MNA:-6.4), Rutin (3HEM:-7.8, 4OTK:-7.5, 2QO0:-9.1, 2AQ1:9.3 and 6MNA:-6.9) and Isoquercitrin (3HEM:-7.3, 4OTK:-6.6, 2QO0:-7.7, 2AQ1:8.3 and 6MNA:-6.6) shows promising activity against all the five target proteins. Further molecular dynamics studies of Petunidin-3-rutinoside with three target proteins 3HEM, 2AQ1 and 2QO0 resulted with low values of average RMSD (3.723 Å, 3.261 Å, and 2.497 Å, respectively) show that the complexes have better conformational stability. The wet lab validation of the current study will pave the new dimensions for the cure of TB patients.Communicated by Ramaswamy H. Sarma.

DOI: 10.1080/07391102.2023.2209648
PMID: 37154535

69. Swimming against the STREAM: Why STREAM 2 data cannot be easily applied to MDR-TB patients across India.

Lung India. 2023 May-Jun;40(3):290-291. doi: 10.4103/lungindia.lungindia_74_23.

Udwadia ZF(1), Patel JM(1), Batyala M(1), Tornheim JA(2), Rodrigues C(3).

DOI: 10.4103/lungindia.lungindia_74_23
PMID: 37148033

70. Bedaquiline and Delamanid: Salvage Therapy in Mycobacterium avium Infection With Treatment Failure.

Arch Bronconeumol. 2023 May;59(5):328-329. doi: 10.1016/j.arbres.2023.02.014. Epub 2023 Feb 25.

[Article in English, Spanish]

Albendín-Iglesias H(1), Caminero JA(2), Galera Peñaranda C(3).

DOI: 10.1016/j.arbres.2023.02.014
PMID: 36894473 [Indexed for MEDLINE]