PubMed Open Access

1. Clofazimine: A journey of a drug.

Biomed Pharmacother. 2023 Nov;167:115539. doi: 10.1016/j.biopha.2023.115539. Epub 2023 Sep 22.

Xu J(1), Koval A(1), Katanaev VL(2).

Among different strategies to develop novel therapies, drug repositioning (aka repurposing) aims at identifying new uses of an already approved or investigational drug. This approach has the advantages of availability of the extensive pre-existing knowledge of the drug's safety, pharmacology and toxicology, manufacturing and formulation. It provides advantages to the risk-versus-rewards trade-off as compared to the costly and time-consuming de novo drug discovery process. Clofazimine, a red-colored synthetic derivative of riminophenazines initially isolated from lichens, was first synthesized in the 1950 s, and passed through several phases of repositioning in its history as a drug. Being initially developed as an anti-tuberculosis treatment, it was repurposed for the treatment of leprosy, prior to re-repositioning for the treatment of multidrug-resistant tuberculosis and other infections. Since 1990 s, reports on the anticancer properties of clofazimine, both in vitro and in vivo, started to appear. Among the diverse mechanisms of action proposed, the activity of clofazimine as a specific inhibitor of the oncogenic Wnt signaling pathway has recently emerged as the promising targeting mechanism of the drug against breast, colon, liver, and other forms of cancer. Seventy years after the initial discovery, clofazimine's journey as a drug finding new applications continues, serving as a colorful illustration of drug repurposing in modern pharmacology.

DOI: 10.1016/j.biopha.2023.115539
PMID: 37742606 [Indexed for MEDLINE]

Conflict of interest statement: Declaration of Competing Interest The authors declare that they have no conflict of interests.

2. The rare manifestations in tuberculous meningoencephalitis: a review of available literature.

Ann Med. 2023 Dec;55(1):342-347. doi: 10.1080/07853890.2022.2164348.

He RL(1), Liu Y(1), Tan Q(1), Wang L(1).

Aim: Tuberculous meningitis is an infectious disease of the central nervous system caused by Mycobacterium tuberculosis (M. tuberculosis). It mainly involves the meninges and brain

parenchyma, as well as the spinal cord and meninges; Disability and mortality rates are high. In recent years, due to the increase of drug-resistant tuberculosis patients, population mobility and the prevalence of acquired immune deficiency syndrome, the incidence rate of tuberculosis has increased significantly, and tuberculous meningitis has also increased.

Methods: At present, tuberculosis is still a worldwide infectious disease that seriously threatens human health, especially in underdeveloped and developing countries. China is the largest developing country in the world with a large population.

Results: The situation of tuberculosis prevention and control is grim. Its disability rate is the highest in tuberculosis infection. In addition to the common non-specific manifestations, tuberculous meningoencephalitis may also have rare manifestations of stroke, hearing loss and visual loss.

Conclusion: Understanding and timely improvement of corresponding examinations and targeted treatment will help improve the prognosis of patients.

DOI: 10.1080/07853890.2022.2164348
PMCID: PMC9828632
PMID: 36598144 [Indexed for MEDLINE]

Conflict of interest statement: No potential conflict of interest was reported by the author(s).

3. Intricate link between siderophore secretion and drug efflux in Mycobacterium tuberculosis.

Antimicrob Agents Chemother. 2023 Oct 18;67(10):e0162922. doi: 10.1128/aac.01629-22. Epub 2023 Sep 7.

Meikle V(1), Zhang L(1), Niederweis M(1).

Drug-resistant Mycobacterium tuberculosis is a worldwide health-care problem rendering current tuberculosis (TB) drugs ineffective. Drug efflux is an important mechanism in bacterial drug resistance. The MmpL4 and MmpL5 transporters form functionally redundant complexes with their associated MmpS4 and MmpS5 proteins and constitute the inner membrane components of an essential siderophore secretion system of M. tuberculosis. Inactivating siderophore secretion is toxic for M. tuberculosis due to self-poisoning at low-iron conditions and leads to a strong virulence defect in mice. In this study, we show that M. tuberculosis mutants lacking components of the MmpS4-MmpL4 and MmpS5-MmpL5 systems are more susceptible to bedaquiline, clofazimine, and rifabutin, important drugs for treatment of drug-resistant TB. While genetic deletion experiments revealed similar functions of the MmpL4 and MmpL5 transporters in siderophore and drug secretion, complementation experiments indicated that the MmpS4-MmpL4 proteins alone are not sufficient to restore drug efflux in an

M. tuberculosis mutant lacking both operons, in contrast to MmpS5-MmpL5. Importantly, an M. tuberculosis mutant lacking the recently discovered periplasmic Rv0455c protein, which is also essential for siderophore secretion, is more susceptible to the same drugs. These results reveal a promising target for the development of dual-function TB drugs, which might poison M. tuberculosis by blocking siderophore secretion and synergize with other drugs by impairing drug efflux.

DOI: 10.1128/aac.01629-22
PMCID: PMC10583673
PMID: 37676015 [Indexed for MEDLINE]

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

4. Household drug-resistant TB contact tracing in Tajikistan.

Int J Tuberc Lung Dis. 2023 Oct 1;27(10):748-753. doi: 10.5588/ijtld.23.0066.

Rekart ML(1), Aung A(1), Cullip T(2), Mulanda W(1), Mun L(1), Pirmahmadzoda B(3), Kliescokova J(1), Achar J(4), Alvarez JL(2), Sitali N(5), Sinha A(2).

BACKGROUND: Tajikistan has a high burden of rifampicin-resistant TB (RR-TB), with 2,700 new cases estimated for 2021 (28/100,000 population). TB is spread among household members through close interaction and children exposed through household contact progress to disease rapidly and frequently.

METHODS: We retrospectively analysed programmatic data from household contact tracing in Dushanbe over 50 months. We calculated person-years of follow-up, contact tracing yield, number needed to screen (NNS) and number needed to test (NNT) to find one new case, and time to diagnosis.

RESULTS: We screened 6,654 household contacts of 830 RR-TB index cases; 47 new RR-TB cases were detected, 43 in Year 1 and 4 in Years 2 or 3. Ten were aged <5 years; 46/47 had TB symptoms, 34/45 had chest radiographs consistent with TB, 11/35 were Xpert Ultra-positive, 29/32 were tuberculin skin test-positive and 28/47 had positive TB culture and phenotypic drug susceptibility results. The NNS to find one RR-TB case was 141.57 and the NNT was 34.49. The yields for different types of contacts were as follows: 0.7% for screened contacts, 2.9% for tested contacts, 17.0% for symptomatic contacts and 12.1% for symptomatic contacts aged below 5 years.

CONCLUSION: RR-TB household contact tracing was feasible and productive in Tajikistan, a low middle-income country with an inefficient healthcare delivery system.

DOI: 10.5588/ijtld.23.0066

PMCID: PMC10519379
PMID: 37749832 [Indexed for MEDLINE]

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

5. Mixed infections in genotypic drug-resistant Mycobacterium tuberculosis.

Sci Rep. 2023 Oct 10;13(1):17100. doi: 10.1038/s41598-023-44341-x.

Wang L(1), Campino S(1), Phelan J(2), Clark TG(3)(4).

Tuberculosis disease (TB), caused by Mycobacterium tuberculosis, is a major global public health problem, resulting in more than 1 million deaths each year. Drug resistance (DR), including multi-drug (MDR-TB), is making TB control difficult and accounts for 16% of new and 48% of previously treated cases. To further complicate treatment decision-making, many clinical studies have reported patients harbouring multiple distinct strains of M. tuberculosis across the main lineages (L1 to L4). The extent to which drug-resistant strains can be deconvoluted within mixed strain infection samples is understudied. Here, we analysed M. tuberculosis isolates with whole genome sequencing data (n = 50,723), which covered the main lineages (L1 9.1%, L2 27.6%, L3 11.8%, L4 48.3%), with genotypic resistance to isoniazid (HR-TB; n = 9546 (29.2%)), rifampicin (RR-TB; n = 7974 (24.4%)), and at least MDR-TB (n = 5385 (16.5%)). TB-Profiler software revealed 531 (1.0%) isolates with potential mixed sub-lineage infections, including some with DR mutations (RR-TB 21/531; HR-TB 59/531; at least MDR-TB 173/531). To assist with the deconvolution of such mixtures, we adopted and evaluated a statistical Gaussian Mixture model (GMM) approach. By simulating 240 artificial mixtures of different ratios from empirical data across L1 to L4, a GMM approach was able to accurately estimate the DR profile of each lineage, with a low error rate for the estimated mixing proportions (mean squared error 0.012) and high accuracy for the DR predictions (93.5%). Application of the GMM model to the clinical mixtures (n = 531), found that 33.3% (188/531) of samples consisted of DR and sensitive lineages, 20.2%(114/531) consisted of lineages with only DR mutations, and 40.6% (229/531) consisted of lineages with genotypic pan-susceptibility. Overall, our work demonstrates the utility of combined whole genome sequencing data and GMM statistical analysis approaches for providing insights into mono and mixed M. tuberculosis infections, thereby potentially assisting diagnosis, treatment decision-making, drug resistance and transmission mapping for infection control.

DOI: 10.1038/s41598-023-44341-x
PMCID: PMC10564873
PMID: 37816829 [Indexed for MEDLINE]

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

6. Treatment of drug-resistant tuberculosis in children and young adolescents in Brazil.

J Clin Tuberc Other Mycobact Dis. 2023 Aug 2;33:100388. doi: 10.1016/j.jctube.2023.100388. eCollection 2023 Dec.

Bruzadelli Paulino da Costa F(1), Zamboni Berra T(1), Garcia de Almeida Ballestero J(1), Bartholomay Oliveira P(2), Maria Pelissari D(3), Mathias Alves Y(1), Carlos Vieira Ramos A(1), Queiroz Rocha de Paiva J(4), Kehinde Ayandeyi Teibo T(1), Alexandre Arcêncio R(1).

INTRODUCTION: Drug-resistant tuberculosis (DR-TB) is a global threat and a challenge for public health authorities worldwide. In children, the diagnosis is even more challenging and DR-TB is poorly described in the literature, as are its treatment outcomes. In this study, we aimed to describe the treatment of drug-resistant TB in children and young adolescents in Brazil.

METHODS: A descriptive epidemiological study of treatment for DR-TB in children under 15 years of age in Brazil between 2013 and 2020. The primary data source was the Information System for Special Tuberculosis Treatments (SITE-TB). Categorical variables were analyzed using relative frequencies (%) and continuous variables by measures of central tendency to characterize the profile of the cases, namely: sociodemographic, clinical characteristics, procedures, tests performed and treatment success. In order to verify the distribution of cases, a spatial analysis was carried out based on the municipality where the cases resided.

RESULTS: Between 2013 and 2020, 19,757 tuberculosis (TB) cases occurred in children aged <15 years in Brazil, and 46 cases of treatment for DR-TB were reported during the same period (annual average of 6 cases). Of these, 73.9% were aged 10-14, 65.2% were male, 4.3% were HIV+ and 43.3% were underweight (BMI<18.5) at the start of treatment. 17.4% had previous contact with TB, 69.6% had primary resistance, 47.8% multidrug resistance. The median duration of treatment was 15 months. DOT and standardized treatment regimen were performed in 52.2% of cases. Bacilloscopy was performed for 97.8% (57.8% positive); culture for 89.1% (75.6% positive), rapid molecular test for 73.9% with proven resistance to rifampicin in 55.8%. Susceptibility testing revealed resistance mainly to isoniazid (87.8%) and rifampicin (60.6%). 73.9% of cases were successfully treated and one death was reported. Cases were treated in 26 Brazilian municipalities, with the majority in Rio de Janeiro (15) and São Paulo (4).

CONCLUSION: DR-TB treatment was recorded in <1% of general TB cases in children and young adolescents, suggesting underreporting of drug-resistant cases in the country. Despite the low number of registered cases, the data reflect the situation of DR-TB in this population and describe important aspects of the problem, as the child needs comprehensive, individualized care, with support from different professionals. We recommend a strengthening of the

country's referral services for the care of children with DR-TB so that surveillance and health care services can work together to identify and follow up cases.

DOI: 10.1016/j.jctube.2023.100388
PMCID: PMC10425933
PMID: 37588725

Conflict of interest statement: The authors declare that they have no known competing financial interests or personal relationships that might appear to influence the work reported in this article.Although the cited agencies supported the research, the funders had no role in the study design; in the collection, analysis, and interpretation of the data; and in the decision to submit the article for publication.

7. Tuberculosis presentation and outcomes in older Hispanic adults from Tamaulipas, Mexico.

Medicine (Baltimore). 2023 Oct 13;102(41):e35458. doi: 10.1097/MD.0000000000035458.

Medrano BA(1), Lee M(1), Gemeinhardt G(2), Rodríguez-Herrera JE(3), García-Viveros M(3), Restrepo BI(1)(4)(5).

Older people are at high risk of developing and dying from pulmonary infections like tuberculosis (TB), but there are few studies among them, particularly in Hispanics. To address these gaps, we sought to identify host factors associated with TB and adverse treatment outcomes in older Hispanics by conducting a cross-sectional study of TB surveillance data from Tamaulipas, Mexico (2006-2013; n = 8381). Multivariable logistic regressions were assessed for older adults (OA ≥65 years) when compared to young (YA, 18-39 years) and middle-aged adults (40-64 years). We found that the OA had features associated with a less complicated TB (e.g., lower prevalence of extra-pulmonary TB and less likely to abandon treatment or have drug resistant TB), and yet, were more likely to die during TB treatment (adj-OR 3.9, 95% 2.5, 5.25). Among the OA, excess alcohol use and low body mass index increased their odds of death during TB treatment, while a higher number of reported contacts (social support) was protective. Diabetes was not associated with adverse outcomes in OA. Although older age is a predictor of death during TB disease, OA are not prioritized by the World Health Organization for latent TB infection screening and treatment during contact investigations. With safer, short-course latent TB infection treatment available, we propose the inclusion of OA as a high-risk group in latent TB management guidelines.

DOI: 10.1097/MD.0000000000035458

PMCID: PMC10578661
PMID: 37832052 [Indexed for MEDLINE]

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

8. Clinical features, resistance patterns and treatment outcomes of drug-resistant extra-pulmonary tuberculosis: A scoping review.

J Clin Tuberc Other Mycobact Dis. 2023 Aug 4;33:100390. doi: 10.1016/j.jctube.2023.100390. eCollection 2023 Dec.

Miiro E(1), Olum R(2), Baluku JB(3)(4).

BACKGROUND: Drug-resistant tuberculosis (DR-TB) is a threat to tuberculosis (TB) control. Extra-pulmonary forms of DR-TB (DR-epTB) are not well characterized. This review summarizes the clinical features, resistance patterns and treatment outcomes of DR-epTB.

METHODS: We searched EMBASE to identify studies that reported drug-resistance among extra-pulmonary TB sites. All age groups were included in this review. Studies which did not describe drug-resistance patterns at extra-pulmonary TB sites were excluded. We summarized the proportion of resistance to individual anti-TB drugs as well as multi-drug resistant (MDR), pre-extensively drug resistant (pre-XDR) and extensively drug-resistant (XDR) TB.

RESULTS: Eighteen studies with a total of 10,222 patients with extra-pulmonary TB of whom 1,236 (12.0%) had DR-epTB, were included in this review. DR-epTB was mostly reported in young people aged 28 to 46 years. While TB meningitis is the most commonly studied form, adenitis is the commonest form of DR-epTB reported in 21% to 47%. Central nervous system TB (3.8% to 51.6%), pleural TB (11.3% to 25.9%), skeletal TB (9.4% to 18.1%), abdominal TB (4.3% to 6.5%), and disseminated TB (3.8%) are also encountered. The HIV co-infection rate is reported to be 5.0% to 81.3% while 2.6% to 25.4 % have diabetes mellitus. Clinical symptoms of DR-epTB are consistent with morbidity in the affected body system. Among patients with DR-epTB, the proportion of MDR TB was 5% to 53% while that for pre-XDR TB and XDR TB was 3% to 40% and 4% to 33%, respectively. Treatment success is achieved in 26% to 83% of patients with DR-epTB while death, treatment loss-to-follow up, and treatment failure occur in 2% to 76%, 7% to 15%, and 0% to 4% respectively. Patients with DR-epTB were reported to have poorer outcomes than those with pulmonary DR-TB and extra-pulmonary drug-susceptible TB.

CONCLUSION: Clinical features of DR-epTB are similar to those observed among people with drug-susceptible EPTB but patients with DR-epTB post worse treatment outcomes.

DOI: 10.1016/j.jctube.2023.100390
PMCID: PMC10425399
PMID: 37588726

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.

9. Bifurcation analysis of a tuberculosis progression model for drug target identification.

Sci Rep. 2023 Oct 16;13(1):17567. doi: 10.1038/s41598-023-44569-7.

Flores-Garza E(1), Hernández-Pando R(2), García-Zárate I(3), Aguirre P(4), Domínguez-Hüttinger E(5).

Tuberculosis (TB) is a major cause of morbidity and mortality worldwide. The emergence and rapid spread of drug-resistant M. tuberculosis strains urge us to develop novel treatments. Experimental trials are constrained by laboratory capacity, insufficient funds, low number of laboratory animals and obsolete technology. Systems-level approaches to quantitatively study TB can overcome these limitations. Previously, we proposed a mathematical model describing the key regulatory mechanisms underlying the pathological progression of TB. Here, we systematically explore the effect of parameter variations on disease outcome. We find five bifurcation parameters that steer the clinical outcome of TB: number of bacteria phagocytosed per macrophage, macrophages death, macrophage killing by bacteria, macrophage recruitment, and phagocytosis of bacteria. The corresponding bifurcation diagrams show all-or-nothing dose-response curves with parameter regions mapping onto bacterial clearance, persistent infection, or history-dependent clearance or infection. Importantly, the pathogenic stage strongly affects the sensitivity of the host to these parameter variations. We identify parameter values corresponding to a latent-infection model of TB, where disease progression occurs significantly slower than in progressive TB. Two-dimensional bifurcation analyses uncovered synergistic parameter pairs that could act as efficient compound therapeutic approaches. Through bifurcation analysis, we reveal how modulation of specific regulatory mechanisms could steer the clinical outcome of TB.

DOI: 10.1038/s41598-023-44569-7
PMCID: PMC10579266
PMID: 37845271 [Indexed for MEDLINE]

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

10. Identifying patients with multidrug-resistant tuberculosis who may benefit from shorter durations of treatment.

PLoS One. 2023 Oct 5;18(10):e0292106. doi: 10.1371/journal.pone.0292106. eCollection 2023.

Winters N(1), Schnitzer ME(1)(2)(3), Campbell JR(4)(5)(6), Ripley S(1), Winston C(7), Savic R(8)(9), Ahmad N(10), Bisson G(11), Dheda K(12), Esmail A(12), Gegia M(13), Monedero I(14), Dalcolmo MP(15), Rodrigues D(16), Singla R(17), Yim JJ(18), Menzies D(1)(5).

OBJECTIVE: Studying treatment duration for rifampicin-resistant and multidrug-resistant tuberculosis (MDR/RR-TB) using observational data is methodologically challenging. We aim to present a hypothesis generating approach to identify factors associated with shorter duration of treatment.

STUDY DESIGN AND SETTING: We conducted an individual patient data meta-analysis among MDR/RR-TB patients restricted to only those with successful treatment outcomes. Using multivariable linear regression, we estimated associations and their 95% confidence intervals (CI) between the outcome of individual deviation in treatment duration (in months) from the mean duration of their treatment site and patient characteristics, drug resistance, and treatments used.

RESULTS: Overall, 6702 patients with successful treatment outcomes from 84 treatment sites were included. We found that factors commonly associated with poor treatment outcomes were also associated with longer treatment durations, relative to the site mean duration. Use of bedaquiline was associated with a 0.51 (95% CI: 0.15, 0.87) month decrease in duration of treatment, which was consistent across subgroups, while MDR/RR-TB with fluoroquinolone resistance was associated with 0.78 (95% CI: 0.36, 1.21) months increase.

CONCLUSION: We describe a method to assess associations between clinical factors and treatment duration in observational studies of MDR/RR-TB patients, that may help identify patients who can benefit from shorter treatment.

DOI: 10.1371/journal.pone.0292106
PMCID: PMC10553332

PMID: 37797071

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

11. Discrepancy in the transmissibility of multidrug-resistant mycobacterium tuberculosis in urban and rural areas in China.

Emerg Microbes Infect. 2023 Dec;12(1):2192301. doi: 10.1080/22221751.2023.2192301.

Li M(1)(2), Lu L(3), Guo M(4), Jiang Q(5), Xia L(6), Jiang Y(7), Zhang S(6), Qiu Y(4), Yang C(1)(8), Chen Y(1)(2), Hong J(3), Guo X(3), Takiff H(9), Shen X(7), Chen C(6), Gao Q(1)(2).

The fitness of multidrug-resistant tuberculosis (MDR-TB) is thought to be an important determinant of a strain's ability to be transmitted. Studies in the laboratory have demonstrated that MDR-TB strains have reduced fitness but the relative transmissibility of MDR-TB versus drug-susceptible (DS) TB strains in human populations remains unresolved. We used data on genomic clustering from our previous molecular epidemiological study in Songjiang (2011-2020) and Wusheng (2009-2020), China, to compare the relative transmissibility of MDR-TB versus DS-TB. Genomic clusters were defined with a threshold distance of 12-single-nucleotide-polymorphisms and the risk for MDR-TB clustering was analyzed by logistic regression. In total, 2212 culture-positive pulmonary TB patients were enrolled in Songjiang and 1289 in Wusheng. The clustering rates of MDR-TB and DS-TB strains were 19.4% (20/103) and 26.3% (509/1936), respectively in Songjiang, and 43.9% (29/66) and 26.0% (293/1128) in Wusheng. The risk of MDR-TB clustering was 2.34 (95% CI 1.38-3.94) times higher than DS-TB clustering in Wusheng and 0.64 (95% CI 0.38-1.06) times lower in Songjiang. Neither lineage 2, compensatory mutations nor rpoB S450L were significantly associated with MDR-TB transmission, and katG S315 T increased MDR-TB transmission only in Wusheng (OR 5.28, 95% CI 1.42-19.21). MDR-TB was not more transmissible than DS-TB in either Songjiang or Wusheng. It appears that the different transmissibility of MDR-TB in Songjiang and Wusheng is likely due to differences in the quality of the local TB control programmes. Suggesting that the most effective way to control MDR-TB is by improving local TB control programmes.

DOI: 10.1080/22221751.2023.2192301
PMCID: PMC10062220
PMID: 36924242 [Indexed for MEDLINE]

Conflict of interest statement: No potential conflict of interest was reported by the author(s).

12. Pretomanid resistance: An update on emergence, mechanisms and relevance for clinical practice.

Int J Antimicrob Agents. 2023 Oct;62(4):106953. doi: 10.1016/j.ijantimicag.2023.106953. Epub 2023 Aug 16.

Nguyen TVA(1), Nguyen QH(1), Nguyen TNT(2), Anthony RM(3), Vu DH(2), Alffenaar JC(4).

Pretomanid (PA-824), a novel anti-tuberculosis (TB) nitroimidazoxazine, has been approved for multi-drug-resistant TB treatment for a few years. Pretomanid has been demonstrated to be highly active against Mycobacterium tuberculosis when combined with other anti-TB drugs. This review provides an update of the current knowledge on the modes of action, resistance mechanisms, emergence of drug resistance, and status of antimicrobial susceptibility testing for pretomanid and its relevance for clinical practice. Pretomanid resistance has been reported in in-vitro and animal models but not yet in clinical trials. Pretomanid-resistance-associated mutations have been reported in the fbiA, fbiB, fbiC, fbiD, ddn and fgd1 genes. However, understanding of in-vivo molecular resistance mechanisms remains limited, and complicates the development of accurate antimicrobial susceptibility testing methods for pretomanid. As such, no reference method for antimicrobial susceptibility testing of pretomanid has been established to guide clinical use. Further studies linking specific mutations, in-vitro susceptibility, drug exposure and resistance mechanisms to treatment failure with pretomanid should be prioritized.

DOI: 10.1016/j.ijantimicag.2023.106953
PMID: 37595848 [Indexed for MEDLINE]

13. The safety and efficacy of decortication for stage III drug-resistant tuberculous empyema.

Interdiscip Cardiovasc Thorac Surg. 2023 Oct 9:ivad166. doi: 10.1093/icvts/ivad166. Online ahead of print.

Yao L(1), Wang B(1), Chen X(1), Liu Q(1), Sheng J(1), Liu X(1), Dai X(1), Jiang Y(1).

OBJECTIVES: This study aimed to evaluate the safety and efficacy of decortication for stage III drug-resistant tuberculous empyema (TE).

METHODS: We analyzed all patients with stage III TE who underwent decortication between March 2015 and October 2019 at Wuhan Pulmonary Hospital. The patients were divided into two groups according to drug-susceptibility testing of bronchoscopy lavage fluid, pleural effusion and tissue specimens, including a drug-resistant group and a drug-sensitive group. We collected and comparatively analyzed the preoperative, perioperative, and postoperative data of the two groups to evaluate the safety and efficacy of decortication for stage III drug-resistant TE.

RESULTS: In total, 135 cases met the inclusion criteria and were enrolled, including 30 cases in the drug-resistant group and 105 cases in the drug-sensitive group. No mortalities were recorded for the entire study population. Compared to the drug-sensitive group, the drug-resistant group was associated with a longer operation time (259.8 ± 78.4 min vs 187.2 ± 56.0 min, p = 0.00), a larger volume of intraoperative blood loss (300 [200,400］ ml vs 200 [130, 300］ ml, p = 0.00) and a higher intraoperative transfusion rate (5/30, 16.7% vs 4/105, 3.8%, p = 0.04). The rate of complications was significantly higher in the drug-resistant group (23; 76.7%) than in the drug-sensitive group (53; 50.5%) (p = 0.01). Recurrence was not reported in any of the patients. Twenty-three (76.7%) patients in the drug-resistant group and 90 (85.7%) patients in the drug-resistant group recovered to an "Excellent" level, and three cases in each group recovered to an "Poor" level; there was no significant difference between the two groups in surgical effects (p = 0.21).

CONCLUSIONS: Decortication is a safe, effective and feasible option for patients with stage III drug-resistant TE, although the operation is difficult and risky.

DOI: 10.1093/icvts/ivad166
PMID: 37812210

14. Designing molecular diagnostics for current tuberculosis drug regimens.

Emerg Microbes Infect. 2023 Dec;12(1):2178243. doi: 10.1080/22221751.2023.2178243.

Georghiou SB(1), de Vos M(1), Velen K(1), Miotto P(2), Colman RE(1)(3), Cirillo

DM(2), Ismail N(4), Rodwell TC(1)(3), Suresh A(1), Ruhwald M(1).

Diagnostic development must occur in parallel with drug development to ensure the longevity of new treatment compounds. Despite an increasing number of novel and repurposed anti-tuberculosis compounds and regimens, there remains a large number of drugs for which no rapid and accurate molecular diagnostic option exists. The lack of rapid drug susceptibility testing for linezolid, bedaquiline, clofazimine, the nitroimidazoles (i.e pretomanid and delamanid) and pyrazinamide at any level of the healthcare system compromises the effectiveness of current tuberculosis and drug-resistant tuberculosis treatment regimens. In the context of current WHO tuberculosis treatment guidelines as well as promising new regimens, we identify the key diagnostic gaps for initial and follow-on tests to diagnose emerging drug resistance and aid in regimen selection. Additionally, we comment on potential gene targets for inclusion in rapid molecular drug susceptibility assays and sequencing assays for novel and repurposed drug compounds currently prioritized in current regimens, and evaluate the feasibility of mutation detection given the design of existing technologies. Based on current knowledge, we also propose design priorities for next generation molecular assays to support triage of tuberculosis patients to appropriate and effective treatment regimens. We encourage assay developers to prioritize development of these key molecular assays and support the continued evolution, uptake, and utility of sequencing to build knowledge of tuberculosis resistance mechanisms and further inform rapid treatment decisions in order to curb resistance to critical drugs in current regimens and achieve End TB targets.Trial registration: ClinicalTrials.gov identifier: NCT05117788..

DOI: 10.1080/22221751.2023.2178243
PMCID: PMC9980415
PMID: 36752055 [Indexed for MEDLINE]

Conflict of interest statement: SBG, MdV, KV, REC, TCR, AS and MR are consultants or employees of FIND, the global alliance for diagnostics, a not-for-profit foundation that supports the evaluation of publicly prioritized TB assays and the implementation of WHO-approved (guidance and prequalification) assays using donor grants. FIND has product evaluation agreements with several private sector companies that design diagnostics for TB and other diseases. These agreements strictly define FIND's independence and neutrality with regard to these private sector companies. MR, PM and DMC are members of the NDWG StopTB Partnership. TCR is a cofounder, board member, and shareholder of Verus Diagnostics, a company that was founded with the intent of developing diagnostic assays. Verus Diagnostics was not involved in any way with data collection, analysis or publication of the results, and TCR has not received any financial support from Verus Diagnostics. University of California, San Diego (UCSD) Conflict of Interest office has reviewed and approved TCR's role in Verus

Diagnostics. TCR is a coinventor of a provisional patent for a TB diagnostic assay (provisional patent 63/048.989). TCR is also a coinventor on a patent associated with the processing of TB sequencing data (European Patent Application No. 14840432.0 & USSN 14/912,918), and has agreed to “donate all present and future interest in and rights to royalties from this patent” to UCSD to ensure that he does not receive any financial benefits from this patent.

15. Whole genome sequencing of drug resistance Mycobacterium tuberculosis from extra-pulmonary sites.

Life Sci Alliance. 2023 Aug 17;6(11):e202302076. doi: 10.26508/lsa.202302076. Print 2023 Nov.

Shi T(1), Shou F(2), He Y(3), Zhou K(3), Gao W(3), Nie X(4), Han M(3), Liao C(5), Li T(6).

This study aimed to determinate characteristics of drug resistance Mycobacterium tuberculosis from patients with extra-pulmonary tuberculosis (EPTB). Patients were retrospectively studied from January 2020 to December 2021. All the isolates were cultured, tested drug susceptibility, and detected the gene mutation using whole genome sequencing. The correlations of whole genome sequencing, pattern of DR, patients' distribution, and transmission were analyzed. 111 DR-EPTB isolates included pre-XDR-TB (53.2%), MDR-TB (29.7%), and poly-DR-TB (12.6%). The resistant drugs were INH followed by RFP and SM. The genotypes of 111 strains were lineage 2 and lineage 4. KatG_p.Ser315Thr was main gene mutation for resistance to INH; rpsL_p.Lys43Arg for SM, rpoB_p.Ser450Leu for rifampicin, embB_p.Met306Val for ethambutol, gyrA_p.Asp94Gly for FQs, and pncA_p.Thr76Pro for PZA. The residence was a significant risk factor for cluster transmission by patients and phenotypic DR types of strains for lineage 2 transmission. In the local area of southwest China INH, rifampicin and SM were main drugs in patients with DR-EPTB. KatG_p.Ser315, rpoB_p.Ser450Leu, and rpsL_p.Lys43Arg were main gene mutations. Phenotypic DR types and residence were main risk of transmission.

DOI: 10.26508/lsa.202302076
PMCID: PMC10435967
PMID: 37591723 [Indexed for MEDLINE]

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

16. Perspectives on pregnant women's educational needs to prevent TB complications during pregnancy and the neonatal period. A qualitative study.

BMC Public Health. 2023 Oct 13;23(1):1997. doi: 10.1186/s12889-023-16770-w.

Khoza LB(1), Mulondo SA(2), Lebese RT(2).

BACKGROUND: Tuberculosis (TB) during pregnancy could confer a high risk for maternal and infant morbidity. Literature indicates that the global burden of active TB disease among pregnant women is not well researched. Statistics for South Africa from WHO give an estimated incidence of 360, 000 cases of TB in 2019; 14,000 people became ill with multidrug-resistant TB in 2019, with a rate of 615 per 100,000 population, implying that the cohorts included pregnant women with and without a diagnosis of TB infection. Therefore, the study aims to increase the understanding of the educational needs required to prevent TB complications during pregnancy and the neonatal period in women diagnosed with TB infection.

METHODS: The study used cross-sectional qualitative and descriptive designs to collect data in the clinical setting of the primary health care services of Limpopo Province, South Africa. The population comprised pregnant women diagnosed with TB infection. A non-probability purposive sampling technique was used to sample 2 health centers and 5 clinics in each of the three sampled districts. The targeted sample size was 63 and it was achieved even though data saturation was observed. Individual interviews were conducted, audiotaped, and transcribed. Guided by the study questions, a thematic content analysis of the findings was used. Ethical considerations were also observed.

RESULTS: Despite that pregnant women have general knowledge about TB disease, the knowledge and awareness regarding the prevention of TB complications in pregnancy and the neonatal period, information on TB/HIV and COVID-19 co-infections, and participants' knowledge about other non-infectious diseases that may affect the mother with TB infection and foetus showed a deficit.

CONCLUSION: Pregnant women with TB disease need to be educated on the negative effects of non-adherence to TB treatment during pregnancy and the neonatal period. There is a need to educate pregnant women about the variant signs and symptoms of TB, HIV and COVID-19 infections since there is a misconception that the three diseases are similar. It is important that pregnant mothers diagnosed with TB should start treatment as soon as possible.

DOI: 10.1186/s12889-023-16770-w
PMCID: PMC10576336
PMID: 37833655 [Indexed for MEDLINE]

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

17. Discovery of pyrimidine-tethered benzothiazole derivatives as novel anti-tubercular agents towards multi- and extensively drug resistant Mycobacterium tuberculosis.

J Enzyme Inhib Med Chem. 2023 Dec;38(1):2250575. doi: 10.1080/14756366.2023.2250575.

Hemeda LR(1), El Hassab MA(2), Abdelgawad MA(3)(4), Khaleel EF(5), Abdel-Aziz MM(6), Binjubair FA(7), Al-Rashood ST(7), Eldehna WM(8)(9), El-Ashrey MK(2)(10).

In this study, new benzothiazole-pyrimidine hybrids (5a-c, 6, 7a-f, and 8-15) were designed and synthesised. Two different functionalities on the pyrimidine moiety of lead compound 4 were subjected to a variety of chemical changes with the goal of creating various functionalities and cyclisation to further elucidate the target structures. The potency of the new molecules was tested against different tuberculosis (TB) strains. The results indicated that compounds 5c, 5b, 12, and 15 (MIC = 0.24-0.98 μg/mL) are highly active against the first-line drug-sensitive strain of Mycobacterium tuberculosis (ATCC 25177). Thereafter, the anti-tubercular activity was evaluated against the two drug-resistant TB strains; ATCC 35822 and RCMB 2674, where, many compounds exhibited good activity with MIC = 0.98-62.5 3 μg/mL and 3.9-62.5 μg/mL, respectively. Compounds 5c and 15 having the highest anti-tubercular efficiency towards sensitive strain, displayed the best activity for the resistant strains by showing the MIC = 0.98 and 1.95 μg/mL for MDR TB, and showing the MIC = 3.9 and 7.81 μg/mL for XDR TB, consecutively. Finally, molecular docking studies were performed for the two most active compounds 5c and 15 to explore their enzymatic inhibitory activities.

DOI: 10.1080/14756366.2023.2250575
PMCID: PMC10472891
PMID: 37649381 [Indexed for MEDLINE]

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

18. Call for special attention to the caregiver burden of patients with drug-resistant tuberculosis in low- and middle-income countries.

Biosci Trends. 2023 Oct 14. doi: 10.5582/bst.2023.01243. Online ahead of print.

Wu S(1), Zhang H(1), Wang Y(1), Wang J(1), Zhang P(1), Asakawa T(2), Lin Y(1).

The tuberculosis (TB)-related caregiver burden (CB), and particularly the multidrug and extensively drug-resistant tuberculosis (M/XDR-TB)-related CB, is not rare in caregivers caring for TB patients, especially when a family member is the caregiver. However, the existing studies on this topic are insufficient. This study briefly summarized the risk factors for the imposition of a TB-related CB and reasons why caregivers for patients with M/XDR-TB are more susceptible to a CB. We propose that special measures should be implemented to alleviate the TB-related CB based on our clinical experience and insights from China. This may improve the situation of caregivers for TB patients and ultimately improve the quality of life of TB patients.

DOI: 10.5582/bst.2023.01243
PMID: 37839889

19. Establishing proof of concept for utility of Trueprep(®)-extracted DNA in line-probe assay testing.

Int J Tuberc Lung Dis. 2023 Oct 1;27(10):742-747. doi: 10.5588/ijtld.23.0003.

Rajendran P(1), Saini S(2), Kumar N(3), Vashistha H(2), Thiruvengadam K(1), Ramamoorthy T(1), Gopalaswamy R(1), Kayesth J(2), Alavadi U(4), Moore M(2), Joshi RP(3), Ramachandran R(5), Anand S(5), Shanmugam S(1), Padmapriyadarsini C(1).

BACKGROUND AND OBJECTIVES: With an increased demand for rapid, diagnostic tools for TB and drug resistance detection, Truenat® MTB-RIF assay has proven to be a rapid point of care molecular test. The present study aimed to establish a proof of concept of using Trueprep-extracted DNA for line-probe assay (LPA) testing.

METHODS: A total of 150 sputum samples (MTB-positive at Truenat sites) were divided into two aliquots. One aliquot was used for DNA extraction using the Trueprep device and MTB testing. The second aliquot of the sample was subjected to GenoLyse® DNA extraction. DNA from both the Trueprep and GenoLyse methods was subjected to first-line (FL) and second-line (SL) LPA testing.

RESULTS: Of 139 Trueprep-extracted DNA, respectively 135 (97%) and 105 (75%) had interpretable results by FL and SL-LPA testing. Of 128 GenoLyse-extracted DNA, all 128 (100%) had interpretable FL-LPA results and 114 (89%) had interpretable SL-LPA results.

CONCLUSION: The results obtained in this study indicate that Trueprep-extracted DNA can be used in obtaining valid LPA results. However, the study needs to be conducted on a larger sample size before our recommendations can be used for policy-making decisions.

DOI: 10.5588/ijtld.23.0003
PMCID: PMC10519390
PMID: 37749831 [Indexed for MEDLINE]

20. Survival status and risk factors for mortality among multidrug-resistant tuberculosis patients in Addis Ababa, Ethiopia: A retrospective follow-up study.

J Clin Tuberc Other Mycobact Dis. 2023 Sep 19;33:100398. doi: 10.1016/j.jctube.2023.100398. eCollection 2023 Dec.

Getahun GK(1), Gezahegn E(2), Endazenawe G(3), Shitemaw T(2), Negash Z(3), Dessu S(4).

BACKGROUND: Tuberculosis continues to be a major health concern around the world. It kills an estimated 1.6 million people each year. The World Health Organization (WHO) removed Ethiopia from its list of thirty countries having a high prevalence of MDR/RR-TB in 2021. As a result, the aim of this study was to assess the current context of survival status and risk factors of multidrug-resistant tuberculosis patients in Addis Ababa, Ethiopia, in 2022.

METHODS: An institutional-based retrospective cohort study with 245 patients was undertaken using multidrug-resistant tuberculosis patients who were recruited from January 1st, 2018 to December 30th, 2021, in St. Peter's specialized hospital. To find independent predictors of survival status, Cox regression analysis was used. An adjusted hazard ratio with a 95% confidence interval and a p-value of < 0.05 was used to establish association and statistical significance.

RESULTS: The result of the study revealed that the incidence of mortality in this study was 13.1% (95% CI: 10.3-16.5). Moreover, being male (AOR = 3.7: 95% CI = 1.2, 11.4), old age (AOR = 14: 95% CI = 3.0, 60.4), site of TB (AOR = 0.2: 95% CI = 0.03, 0.6), and presence of comorbidity (AOR = 9.2: 95% CI = 2.4, 35.3), were independent predictors of time to death.

CONCLUSION: Generally, the death rate among research participants was high. Moreover, male gender, old age, site of tuberculosis, and presence of other comorbidity were predictors of mortality among MDR-TB patients.

DOI: 10.1016/j.jctube.2023.100398
PMCID: PMC10520522
PMID: 37767135

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. Global burden of disease due to rifampicin-resistant tuberculosis: a mathematical modeling analysis.

Nat Commun. 2023 Oct 4;14(1):6182. doi: 10.1038/s41467-023-41937-9.

Menzies NA(1)(2), Allwood BW(#)(3), Dean AS(#)(4), Dodd PJ(#)(5), Houben RMGJ(#)(6)(7), James LP(#)(8)(9), Knight GM(#)(10), Meghji J(#)(11), Nguyen LN(#)(4), Rachow A(#)(12)(13)(14), Schumacher SG(#)(4), Mirzayev F(4), Cohen T(15).

In 2020, almost half a million individuals developed rifampicin-resistant tuberculosis (RR-TB). We estimated the global burden of RR-TB over the lifetime of affected individuals. We synthesized data on incidence, case detection, and treatment outcomes in 192 countries (99.99% of global tuberculosis). Using a mathematical model, we projected disability-adjusted life years (DALYs) over the lifetime for individuals developing tuberculosis in 2020 stratified by country, age, sex, HIV, and rifampicin resistance. Here we show that incident RR-TB in 2020 was responsible for an estimated 6.9 (95% uncertainty interval: 5.5, 8.5) million DALYs, 44% (31, 54) of which accrued among TB survivors. We estimated an average of 17 (14, 21) DALYs per person developing RR-TB, 34% (12, 56) greater than for rifampicin-susceptible tuberculosis. RR-TB burden per 100,000 was highest in former Soviet Union countries and southern African countries. While RR-TB causes substantial short-term morbidity and mortality, nearly half of the overall disease burden of RR-TB accrues among tuberculosis survivors. The substantial long-term health impacts among those surviving RR-TB disease suggest the need for improved post-treatment care and further justify increased health expenditures to prevent RR-TB transmission.

DOI: 10.1038/s41467-023-41937-9
PMCID: PMC10550952
PMID: 37794037 [Indexed for MEDLINE]

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

22. Isoniazid resistance-conferring mutations are associated with highly variable phenotypic resistance.

J Clin Tuberc Other Mycobact Dis. 2023 Jul 26;33:100387. doi: 10.1016/j.jctube.2023.100387. eCollection 2023 Dec.

Lale Ngema S(1), Dookie N(1), Perumal R(1)(2), Nandlal L(1), Naicker N(1), Peter Letsoalo M(1), O'Donnell M(3), Khan A(1), Padayatchi N(1), Naidoo K(1)(2).

BACKGROUND: High-dose isoniazid is recommended in the 9-12 months short-course regimen for multidrug-resistant tuberculosis with inhA mutation. However, there is insufficient evidence to support the assumption of genotypic-phenotypic concordance. This study aimed to identify the genetic mutations associated with high-level phenotypic isoniazid resistance.

METHODS: Clinical isolates from patients with drug-resistant tuberculosis were profiled by whole-genome sequencing and subjected to minimum inhibitory concentration (MIC) testing using MGIT based-method. MICs were performed in concentration ranges based on the mutation present: isolates with no isoniazid resistance-conferring mutations and H37Rv, 0.016-0.256 µg/ml; inhA, 0.256-4.0 µg/ml, katG 1.0-16.0 µg/ml; and inhA + katG, 4.0-64.0 µg/ml. Isolates demonstrating resistance at the upper limit of the concentration range were tested up to the maximum of 64.0 µg/ml. Bootstrap of the mean MICs was performed to increase the robustness of the estimates and an overlap index was used to compare the distributions of the MICs for each mutation profile.

RESULTS: A total of 52 clinical isolates were included in this analysis. Bootstrap MIC means for inhA, katG and inhA + katG were 33.64 (95% CI, 9.47, 56.90), 6.79 (4.45, 9.70) and 52.34 (42.750, 61.66) µg/ml, respectively. There was high overlap between inhA and inhA + katG mutations (eta = 0.45) but not with inhA and katG (eta = 0.19). Furthermore, katG showed poor overlap with inhA + katG mutations (eta = 0.09). Unexpectedly, 4/8 (50.0%) of all InhA mutants demonstrated high-level resistance, while 20/24 (83.3%) of katG mutants demonstrated moderate-level resistance.

CONCLUSIONS: InhA mutations demonstrated unexpectedly high MICs and showed high overlap with inhA + katG. Contrary to the common belief that katG mutants are associated with high-level resistance, this mutation primarily showed moderate-level resistance.

DOI: 10.1016/j.jctube.2023.100387
PMCID: PMC10405055
PMID: 37554582

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.

23. Risk factor analysis of postoperative complications after adjunctive pulmonary resection in patients with multidrug-resistant tuberculosis: A multi-institutional study.

J Microbiol Immunol Infect. 2023 Oct;56(5):1064-1072. doi: 10.1016/j.jmii.2023.07.006. Epub 2023 Jul 28.

Huang WL(1), Chien ST(2), Yu MC(3), Chang BS(4), Yen YT(5), Wu MH(6), Tseng YL(7).

BACKGROUND AND OBJECTIVE: Multidrug-resistant tuberculosis (MDR-TB) requires extended treatment with regimens with multiple side effects, resulting in high treatment failure rates. Adjunctive lung resection combined with anti-tubercular agents improves outcomes. However, few studies have evaluated the potential harm from surgery and determined the optimal conditions for surgery. We aimed to analyze perioperative conditions to assess risk factors for postoperative complications in a multi-institutional setting.

METHODS: This retrospective study included 44 patients with MDR-TB who underwent adjunctive lung resection at three management groups of the Taiwan MDR-TB consortium between January 2007 and December 2020. Demographic data, clinical characteristics, radiological findings, sputum culture status before surgery, primary or acquired drug resistance, surgical procedure, complications, and treatment outcomes were collected and analyzed. Multivariate logistic regression was used to identify risk factors for postoperative complications.

RESULTS: Twenty-seven patients (61.4%) underwent lung resection using video-assisted thoracic surgery (VATS). The overall surgical complication rate was 20.5%, and the surgical mortality rate was 9.1%. Postsurgical hemothorax was the most common complication (11.4%). According to the univariate analysis, hilum involvement in images, positive preoperative sputum culture, and thoracotomy approach were unfavorable factors. VATS approach [adjusted OR, 0.088 (95% CI, 0.008-0.999)] was the only favorable factor identified by multivariate analysis.

CONCLUSION: The minimally invasive approach is a growing trend, and lobectomies and sublobar resections were the main procedures for MDR-TB. The VATS approach significantly reduced the surgical complication rate. Postsurgical hemothorax was noteworthy, and meticulous hemostasis of the chest wall and residual lung surface is critical for successful resections.

DOI: 10.1016/j.jmii.2023.07.006
PMID: 37586914 [Indexed for MEDLINE]

Conflict of interest statement: Conflicts of interest None declared.

24. Selecting an appropriate all-oral short-course regimen for patients with multidrug-resistant or pre-extensive drug-resistant tuberculosis in China: A multicenter prospective cohort study.

Int J Infect Dis. 2023 Oct;135:101-108. doi: 10.1016/j.ijid.2023.08.001. Epub 2023 Aug 10.

Fu L(1), Zhang X(2), Xiong J(3), Sun F(4), Weng T(4), Li Y(4), Zhang P(1), Li H(1), Yang Q(5), Cai Y(6), Liang H(7), Chen Q(8), Wang Z(1), Liu L(1), Chen X(6), Zhang W(4), Deng G(9).

OBJECTIVES: Long, ineffective, and toxic regimens hinder the treatment of patients with multidrug-resistant tuberculosis (MDR-TB) and pre-extensive drug-resistant tuberculosis (pre-XDR-TB).

METHODS: We conducted a multicenter cohort study to prospectively evaluate the safety and efficacy of three 9-month, all-oral, 5-drug regimens. Regimen A (bedaquiline [Bdq]+linezolid [Lzd]+moxifloxacin [Mfx]+cycloserine [Cs]+pyrazinamide [Pza]) and Regimen B (Lzd+Mfx+Cs+clofazimine [Cfz]+Pza) were used to treat MDR-TB patients (Groups A and B, respectively, assigned according to the patient's treatment preference), while Regimen C (Bdq+Lzd+Cs+Cfz+Pza) was used to treat pre-XDR-TB patients (Group C). The primary endpoint was the occurrence of an unfavorable outcome within 12 months of treatment completion, regardless of regimen.

RESULTS: A total of 104 patients (34 in Group A, 46 in Group B, and 24 in Group C), with a median age of 35.5 (29.0-54.0) years, were included in the analysis population. At 12 months after treatment completion, five patients were deemed non-assessable. Of the remaining 99 participants, seven (7.1%) had an

unfavorable outcome (including two deaths from any cause, four with treatment failure, and one loss to follow-up) and 92 (92.9%) had a favorable outcome. Culture conversion was achieved in 82.5% (80/97) of participants at month 2 and in 97.9% (94/97) of participants at month 6. Adverse events (AEs) resulting in drug adjustment occurred in 69.2% (72/104) of participants, mainly due to Lzd and Pza use. A QT interval prolongation of ≥ 500 ms occurred in 5.8% (6/104) of participants.

CONCLUSION: The primary outcome of the three tailored, 9-month, all-oral, 5-drug regimens was satisfactory in the vast majority of MDR-TB and pre-XDR-TB patients, with manageable and reversible AEs.

DOI: 10.1016/j.ijid.2023.08.001
PMID: 37567554

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

25. Predictive capabilities of baseline radiological findings for early and late disease outcomes within sensitive and multi-drug resistant tuberculosis cases.

Eur J Radiol Open. 2023 Sep 27;11:100518. doi: 10.1016/j.ejro.2023.100518. eCollection 2023 Dec.

Rosenfeld G(1), Gabrielian A(1), Hurt D(1), Rosenthal A(1).

PURPOSE: This study compares performance of Timika Score to standardized, detailed radiologist observations of Chest X rays (CXR) for predicting early infectiousness and subsequent treatment outcome in drug sensitive (DS) or multi-drug resistant (MDR) tuberculosis cases. It seeks improvement in prediction of these clinical events through these additional observations.

METHOD: This is a retrospective study analyzing cases from the NIH/NIAID supported TB Portals database, a large, trans-national, multi-site cohort of primarily drug-resistant tuberculosis patients. We analyzed patient records with sputum microscopy readings, radiologist annotated CXR, and treatment outcome including a matching step on important covariates of age, gender, HIV status, case definition, Body Mass Index (BMI), smoking, drug use, and Timika Score across resistance type for comparison.

RESULTS: 2142 patients with tuberculosis infection (374 with poor outcome and

1768 with good treatment outcome) were retrospectively reviewed. Bayesian ANOVA demonstrates radiologist observations did not show greater predictive ability for baseline infectiousness (0.77 and 0.74 probability in DS and MDR respectively); however, the observations provided superior prediction of treatment outcome (0.84 and 0.63 probability in DS and MDR respectively). Estimated lung abnormal area and cavity were identified as important predictors underlying the Timika Score's performance.

CONCLUSIONS: Timika Score simplifies the usage of baseline CXR for prediction of early infectiousness of the case and shows comparable performance to using detailed, standardized radiologist observations. The score's utility diminishes for treatment outcome prediction and is exceeded by the usage of the detailed observations although prediction performance on treatment outcome decreases especially in MDR TB cases.

DOI: 10.1016/j.ejro.2023.100518
PMCID: PMC10556559
PMID: 37808069

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.

26. Mycobacterium tuberculosis infection depressed cytotoxic T cells activity owing to decreasing NKG2C and increasing NKG2A expression.

Mol Immunol. 2023 Oct;162:133-142. doi: 10.1016/j.molimm.2023.08.014. Epub 2023 Sep 7.

Shen X(1), Wu T(1), Ji X(1), Yang K(2), Wang L(1), Peng Y(3), Huang G(1), Shen H(4), Sha W(5).

Cytotoxic T lymphocytes (CTLs) play protective roles in immunity against tuberculosis (TB) infection by strongly inhibiting intracellular mycobacterial growth. In TB infection, the impairing mechanism of CTLs function remains unclear. In this study, we identified that the cytotoxic granule molecules expression levels of perforin (PRF) and granulysin (GNLY) in CD3+ and CD8+ CTL cells were significantly depressed in TB patients compared to those in healthy donors. The frequencies of T-CTLs, co-expressing granzyme B (GZMB), PRF and GNLY, were obviously decreased in TB patients. Moreover, NKG2C highly expressed in T-CTLs, was an effective activator of cytotoxic activity of CD3+ T cells.

And, NKG2C+CD3+ T cells potently inhibited intracellular mycobacterial growth. The proportions of NKG2C+ cells in CD3+ and CD8+ T cells were dramatically decreased in TB patients. Contrarily, NKG2A, an inhibitor of T cells cytotoxic activities, was highly expressed in T-CTLs of CD3+ and CD8+ T cells in TB patients. Here, we successfully discovered that depressed CTLs activities in TB patients were attributed to low expression of cytotoxic granule molecules and high expression of inhibitory NKG2A receptor, suppression of agonist receptor NKG2C. Thus, NKG2 receptors were potential targets for immunotherapy of tuberculosis, especially for multidrug-resistant tuberculosis.

DOI: 10.1016/j.molimm.2023.08.014
PMID: 37683324 [Indexed for MEDLINE]

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

27. Herp regulates intracellular survival of Mycobacterium tuberculosis H37Ra in macrophages by regulating reactive oxygen species-mediated autophagy.

mBio. 2023 Oct 6:e0153523. doi: 10.1128/mbio.01535-23. Online ahead of print.

Son SH(1)(2), Lee J(1)(2)(3), Cho SN(1)(2), Choi JA(1)(2)(3), Kim J(1)(2), Nguyen TD(1)(2), Lee SA(1)(2), Son D(1)(2), Song CH(1)(2)(3).

Novel treatment strategies for tuberculosis (TB), such as host-directed therapeutics, may offer therapeutic options for patients with drug-resistant TB. Endoplasmic reticulum (ER) stress-mediated apoptosis is one of the host defense mechanisms used to remove mycobacteria. It is reported that homocysteine-inducible ER protein with ubiquitin-like domain 1 (Herp) inhibits apoptosis by preventing the loss of ER Ca2+ and mitochondrial potential during ER stress. However, the roles of Herp in ER stress and apoptosis during H37Ra infection are largely unknown. Here, we show that Herp is induced in H37Ra-infected macrophages through an activating transcription factor 6 (ATF6)-dependent ER stress response. Suppressing Herp by genetic approaches decreased production of HRD1, conserved branch of mammalian ER-associated degradation (ERAD) machinery, and increased the production levels of ER stress-associated molecules such as p-IRE1α and BiP after H37Ra infection. Suppressing Herp also increased both the NADPH oxidase 2 and inositol triphosphate receptor, which sequentially led to increased reactive oxygen species (ROS) production during H37Ra infection. Interestingly, the Herp depletion-mediated ROS increment led to autophagy induction, which led to

decreased intracellular survival of mycobacteria in H37Ra-infected macrophages. The role of Herp was further confirmed by the fact that blocking this molecule in vitro and in vivo significantly reduced mycobacterial survival. These findings indicate that Herp mediates crosstalk between ER stress and ROS-mediated autophagy during H37Ra infection, suggesting the potential of Herp manipulation as a therapeutic strategy for Mycobacterium tuberculosis (Mtb) infection.IMPORTANCESeveral studies have suggested that endoplasmic reticulum (ER) stress is important in the pathogenesis of infectious diseases; however, the precise function of ER stress regulation and the role of Herp as a regulator in Mtb H37Ra-induced ER stress remain elusive. Therefore, our study investigated ER stress and autophagy associated with Herp expression in Mycobacterium tuberculosis-infected macrophages to determine the role of Herp in the pathogenesis of tuberculosis.

DOI: 10.1128/mbio.01535-23
PMID: 37800958

28. Accuracy of the InnowaveDX MTB/RIF test for detection of Mycobacterium tuberculosis and rifampicin resistance: a prospective multicentre study.

Emerg Microbes Infect. 2023 Dec;12(1):2151382. doi: 10.1080/22221751.2022.2151382.

Deng Y(1), Ma Z(2), Su B(3), Bai G(4), Pan J(5), Wang Q(6), Cai L(7), Song Y(8), Shang Y(2), Ma P(3), Li J(4), Zhou Q(5), Mulati G(6), Fan D(7), Li S(2), Tan Y(3), Pang Y(2).

Early and accurate diagnosis of tuberculosis (TB) is necessary to initiate proper therapy for the benefit of the patients and to prevent disease transmission in the community. In this study, we developed the InnowaveDX MTB/RIF (InnowaveDX) to detect Mycobacterium tuberculosis (MTB) and rifampicin resistance simultaneously. A prospective multicentre study was conducted to evaluate the diagnostic performance of InnowaveDX for the detection MTB in sputum samples as compared with Xpert and culture. The calculated limit of detection (LOD) for InnowaveDX was 9.6 CFU/ml for TB detection and 374.9 CFU/ml for RIF susceptibility. None of the other bacteria tested produced signals that fulfilled the positive TB criteria, demonstrating a species-specificity of InnowaveDX. Then 951 individuals were enrolled at 7 hospitals, of which 607 were definite TB cases with positive culture and/or Xpert results, including 354 smear-positive and 253 smear-negative cases. InnowaveDX sensitivity was 92.7% versus bacteriologically TB standard. Further follow-up revealed that 61 (91.0%) out of 67 false-positive patients with no bacteriological evidence met the criteria of clinically diagnosed TB. Among 125 RIF-resistant TB patients

diagnosed by Xpert, 108 cases were correctly identified by InnowaveDX, yielding a sensitivity of 86.4%. Additionally, the proportion of very low bacterial load in the discordant susceptibility group was significantly higher than in the concordant susceptibility group (P = 0.029). To conclude, we have developed a novel molecular diagnostic with promising detection capabilities of TB and RIF susceptibility. In addition, the discordant RIF susceptibility results between InnowaveDX and Xpert are more frequently observed in samples with very low bacterial load.

DOI: 10.1080/22221751.2022.2151382
PMCID: PMC9815255
PMID: 36416478 [Indexed for MEDLINE]

Conflict of interest statement: No potential conflict of interest was reported by the author(s).

29. Advancing tuberculosis management: the role of predictive, preventive, and personalized medicine.

Front Microbiol. 2023 Oct 4;14:1225438. doi: 10.3389/fmicb.2023.1225438. eCollection 2023.

Dohál M(1), Porvazník I(2)(3), Solovič I(2)(3), Mokrý J(4).

Tuberculosis is a major global health issue, with approximately 10 million people falling ill and 1.4 million dying yearly. One of the most significant challenges to public health is the emergence of drug-resistant tuberculosis. For the last half-century, treating tuberculosis has adhered to a uniform management strategy in most patients. However, treatment ineffectiveness in some individuals with pulmonary tuberculosis presents a major challenge to the global tuberculosis control initiative. Unfavorable outcomes of tuberculosis treatment (including mortality, treatment failure, loss of follow-up, and unevaluated cases) may result in increased transmission of tuberculosis and the emergence of drug-resistant strains. Treatment failure may occur due to drug-resistant strains, non-adherence to medication, inadequate absorption of drugs, or low-quality healthcare. Identifying the underlying cause and adjusting the treatment accordingly to address treatment failure is important. This is where approaches such as artificial intelligence, genetic screening, and whole genome sequencing can play a critical role. In this review, we suggest a set of particular clinical applications of these approaches, which might have the potential to influence decisions regarding the clinical management of tuberculosis patients.

DOI: 10.3389/fmicb.2023.1225438
PMCID: PMC10582268
PMID: 37860132

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.

30. Prevalence, risk factors and treatment outcomes of fluoroquinolones-associated tendinopathy in tuberculosis patients at university hospital, Thailand.

Heliyon. 2023 Sep 20;9(10):e20331. doi: 10.1016/j.heliyon.2023.e20331. eCollection 2023 Oct.

Chongboonwatana J(1), Terbsiri V(2), Suwanpimolkul G(2)(3)(4).

BACKGROUND: Tuberculosis (TB) is an epidemic disease in Thailand. Fluoroquinolones are used to treat TB and have a lengthy treatment course. Therefore, many patients may have adverse effects from these medications. Tendinopathy has been reported as a significant adverse effect of fluoroquinolones. Although the mechanism of tendinopathy from fluoroquinolones is not fully understood, it can progress to a more serious consequence such as a ruptured tendon which can result in morbidity if not treated effectively.

METHODS: This study was a single-centered, retrospective descriptive study conducted in patients at a tertiary-level university hospital in Thailand. TB patients who received fluoroquinolones for the treatment of TB from January 2017 to December 2019 were enrolled. This study assessed the prevalence, clinical characteristics, treatment, treatment outcomes for fluoroquinolones-associated tendinopathy, and treatment outcomes of TB.

RESULTS: During the study period, 184 participants that were diagnosed with TB and used fluoroquinolones were enrolled in the study. 34 (18.5%) participants developed tendinopathy. The risk factors that were associated with fluoroquinolones-associated tendinopathy were younger age (<60 years) (Odd ratio (OR) 3.61; 95% CI 1.16-11.23), female (OR 3.54; 95% CI 1.58-7.90), and prolonged usage of levofloxacin (>180 days) (OR 2.61; 95%CI 1.12-6.08). All participants who developed tendinopathy received conservative treatment; the dose of fluoroquinolones was reduced in 9 (26.4%) participants, fluoroquinolones were discontinued in 7 (20.6%) participants and the rest of the participants (n = 18; 52.9%) had conservative treatment. After conservative treatment, 25 (73.5%)

participants recovered from tendinopathy. For the TB treatment, 27 (79.4%) participants in the tendinopathy group completed TB treatment and none of them experienced treatment failure. On the other hand, 89 (59.3%) participants in the no tendinopathy group had completed their TB treatment and 3 (2%) of them experienced treatment failure.

CONCLUSIONS: The prevalence of fluoroquinolones-associated tendinopathy was not uncommon, and the risk of fluoroquinolones-associated tendinopathy was high in young and female patients. Levofloxacin use was related to an elevated risk of developing tendinopathy, which was dose- and duration-dependent. Conservative treatment, reducing the dose or discontinuation of fluoroquinolones successfully improved the symptoms of tendinopathy. Fluoroquinolones-associated tendinopathy did not affect the treatment of TB.

DOI: 10.1016/j.heliyon.2023.e20331
PMCID: PMC10550594
PMID: 37810827

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.

31. Universal drug-susceptibility testing of first-line drugs to preserve their efficacy: An essential strategy to defeat tuberculosis.

J Clin Tuberc Other Mycobact Dis. 2023 Aug 22;33:100394. doi: 10.1016/j.jctube.2023.100394. eCollection 2023 Dec.

Dev Bhattarai M(1).

DOI: 10.1016/j.jctube.2023.100394
PMCID: PMC10475499
PMID: 37671085

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.

PubMed Non-Open Access

32. Toxic neuropathies.

Curr Opin Neurol. 2023 Oct 1;36(5):402-409. doi: 10.1097/WCO.0000000000001193. Epub 2023 Aug 2.

Rossor AM(1), Manji H.

PURPOSE OF REVIEW: Immunotherapy has had a significant impact on the treatment of an increasing number of cancers as well as in inflammatory, rheumatological and gastroenterological conditions.Recreational nitrous oxide use is now a global epidemic. Linezolid is now recommended for the treatment of drug-resistant tuberculosis (TB); neuropathy is a significant cause of morbidity.Global warming will result in increasing toxin exposure, such as ciguatera, in previously unaffected areas.
RECENT FINDINGS: With increasing experience, the pathophysiology underlying the neuropathic complications of these drugs has become clear with guidelines now available, for the complications of immune check-point inhibitors and nitrous oxide toxicity. The optimum dose and duration of treatment for resistant TB with regimens, including linezolid, has been ascertained.
SUMMARY: Although neuropathic complications with immunotherapy are relatively rare, it is essential that they are recognized and treated early. Nitrous oxide toxicity should be in the differential diagnosis for all patients, particularly those of younger age, presenting with a neuropathy or myleo-neuropathy. Ciguatera toxicity is under recognized and its geographical spread will increase due to global warming. Further research is necessary on the mechanisms and treatment of both acute and chronic effects, which at present, are only symptomatic.

DOI: 10.1097/WCO.0000000000001193
PMID: 37639472 [Indexed for MEDLINE]

33. Linezolid optic neuropathy.

Curr Opin Ophthalmol. 2023 Nov 1;34(6):481-486. doi: 10.1097/ICU.0000000000000995. Epub 2023 Aug 21.

Miller HV(1), Cao AA(2), McClelland CM(1)(3), Lee MS(1)(3).

PURPOSE OF REVIEW: In this article, we reviewed 67 reported cases of linezolid optic neuropathy and describe the common characteristics and expectations for recovery with an emphasis on recent findings in the literature.
RECENT FINDINGS: Linezolid classically causes a reversible, duration-dependent

optic neuropathy. However, in our review, we found only 66.7% of patients recovered complete visual function. Vision loss most commonly affected visual acuity followed by visual field and color vision. We also found patients taking higher doses of linezolid experienced full recovery less often, suggesting a dose-dependent component of linezolid optic neuropathy. Linezolid use has increased in frequency and duration, especially in the treatment of drug-resistant tuberculosis, and data indicate that these patients experience lower rates of complete vision recovery compared with patients taking linezolid for other indications.
SUMMARY: Linezolid is an effective medication for treating drug-resistant infections; however, it may result in optic neuropathy. It is reasonable for patients on linezolid to undergo screening examinations, especially those on higher doses or for prolonged duration of therapy.

DOI: 10.1097/ICU.0000000000000995
PMID: 37603423 [Indexed for MEDLINE]

34. Successful Multidrug-Resistant Tuberculosis Treatment Without HIV Viral Suppression: A Missed Opportunity.

J Acquir Immune Defic Syndr. 2023 Nov 1;94(3):253-261. doi: 10.1097/QAI.0000000000003268.

Geiger K(1)(2), Patil A(2), Budhathoki C(1), Dooley KE(3), Lowensen K(2), Ndjeka N(4)(5), Ngozo J(6), Farley JE(1)(2).

BACKGROUND: Coinfection with multidrug-resistant tuberculosis (MDR-TB) and HIV is common, but few published studies examine how undergoing MDR-TB treatment affects HIV disease indicators.

METHODS: Using data from a nested, retrospective cohort of people with HIV (PWH) and successful MDR-TB treatment outcomes, we built multivariable regression models to explore correlates of HIV viral suppression at MDR-TB treatment completion.

RESULTS: Among 531 PWH successfully treated for MDR-TB, mean age was 37.4 years (SD 10.2, interquartile range 30-43), 270 (50.8%) were male, 395 (74.4%) were virally suppressed at MDR-TB outcome, and 259 (48.8%) took bedaquiline. Older age (adjusted odds ratio [aOR] 1.04, 95% confidence interval [CI]: 1.01 to 1.06) increased odds of viral suppression, while having a prior TB episode (aOR 0.45, 95% CI: 0.31 to 0.64), having a detectable viral load at MDR-TB treatment initiation (aOR 0.17, 95% CI: 0.09 to 0.30), living in a township (aOR 0.49, 95%

CI: 0.28 to 0.87), and being changed from efavirenz-based antiretroviral therapy (ART) to a protease inhibitor due to bedaquiline usage (aOR 0.19, 95% CI: 0.04 to 0.82) or not having an ART change while on bedaquiline (aOR 0.29, 95% CI: 0.11 to 0.75) lowered odds of viral suppression. Changing from efavirenz to nevirapine due to bedaquiline usage did not significantly affect odds of viral suppression (aOR 0.41, 95% CI: 0.16 to 1.04).

CONCLUSIONS: Increased pill burden and adverse treatment effects did not significantly affect HIV viral suppression while switching ART to a protease inhibitor to accommodate bedaquiline or not changing ART while taking bedaquiline did, suggesting that PWH and MDR-TB may benefit from additional support if they must switch ART.

DOI: 10.1097/QAI.0000000000003268
PMID: 37757847 [Indexed for MEDLINE]

Conflict of interest statement: The authors have no funding or conflicts of interest to disclose.

35. Bedaquiline, Pretomanid, and Linezolid for Multidrug-Resistant Tuberculosis Treatment in the United States: A BIG Deal.

Clin Infect Dis. 2023 Oct 5;77(7):1063-1064. doi: 10.1093/cid/ciad314.

Acuña-Villaorduña C(1)(2), Sinha P(1)(2).

Comment on
Clin Infect Dis. 2023 Oct 5;77(7):1053-1062.

DOI: 10.1093/cid/ciad314
PMID: 37249072

Conflict of interest statement: Potential conflicts of interest. The authors: No reported conflicts of interest. Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

36. Long-term outcomes after tuberculosis for people with HIV in eastern Europe.

AIDS. 2023 Nov 1;37(13):1997-2006. doi: 10.1097/QAD.0000000000003670. Epub 2023 Jul 27.

Kraef C(1)(2)(3), Bentzon A(1), Roen A(1)(4), Bolokadze N(5), Thompson M(6),

Azina I(7), Tetradov S(8), Skrahina A(9), Karpov I(10), Mitsura V(11), Paduto D(12), Trofimova T(13), Borodulina E(14), Mocroft A(1)(4), Kirk O(1)(2), Podlekareva DN(1)(15); TB:HIV study group.

BACKGROUND: Eastern Europe has a high burden of tuberculosis (TB)/HIV coinfection with high mortality shortly after TB diagnosis. This study assesses TB recurrence, mortality rates and causes of death among TB/HIV patients from Eastern Europe up to 11 years after TB diagnosis.

METHODS: A longitudinal cohort study of TB/HIV patients enrolled between 2011 and 2013 (at TB diagnosis) and followed-up until end of 2021. A competing risk regression was employed to assess rates of TB recurrence, with death as competing event. Kaplan-Meier estimates and a multivariable Cox-regression were used to assess long-term mortality and corresponding risk factors. The Coding Causes of Death in HIV (CoDe) methodology was used for adjudication of causes of death.

RESULTS: Three hundred and seventy-five TB/HIV patients were included. Fifty-three (14.1%) were later diagnosed with recurrent TB [incidence rate 3.1/100 person-years of follow-up (PYFU), 95% confidence interval (CI) 2.4-4.0] during a total follow-up time of 1713 PYFU. Twenty-three of 33 patients with data on drug-resistance (69.7%) had multidrug-resistant (MDR)-TB. More than half with recurrent TB (n = 30/53, 56.6%) died. Overall, 215 (57.3%) died during the follow-up period, corresponding to a mortality rate of 11.4/100 PYFU (95% CI 10.0-13.1). Almost half of those (48.8%) died of TB. The proportion of all TB-related deaths was highest in the first 6 (n = 49/71; 69%; P < 0.0001) and 6-24 (n = 33/58; 56.9%; P < 0.0001) months of follow-up, compared deaths beyond 24 months (n = 23/85; 26.7%).

CONCLUSION: TB recurrence and TB-related mortality rates in PWH in Eastern Europe are still concerningly high and continue to be a clinical and public health challenge.

DOI: 10.1097/QAD.0000000000003670
PMID: 37503671 [Indexed for MEDLINE]

37. Resistance patterns and transmission of mono- and polyresistant TB: clinical impact of WGS.

JAC Antimicrob Resist. 2023 Oct 4;5(5):dlad108. doi: 10.1093/jacamr/dlad108. eCollection 2023 Oct.

Dohál M(1), Dvořáková V(2), Šperková M(2), Pinková M(2), Spitaleri A(3)(4), Rasmussen EM(5), Škereňová M(1)(6), Krivošová M(1), Gondáš E(1), Porvazník I(7)(8), Solovič I(7), Cirillo DM(3), Mokrý J(9).

OBJECTIVES: Rapidly diagnosing drug-resistant TB is crucial for improving treatment and transmission control. WGS is becoming increasingly accessible and has added value to the diagnosis and treatment of TB. The aim of the study was to perform WGS to determine the rate of false-positive results of phenotypic drug susceptibility testing (pDST) and characterize the molecular mechanisms of resistance and transmission of mono- and polyresistant Mycobacterium (M.) tuberculosis.

METHODS: WGS was performed on 53 monoresistant and 25 polyresistant M. tuberculosis isolates characterized by pDST. Sequencing data were bioinformatically processed to infer mutations encoding resistance and determine the origin of resistance and phylogenetic relationship between isolates studied.

RESULTS: The data showed the variable sensitivity and specificity of WGS in comparison with pDST as the gold standard: isoniazid 92.7% and 92.3%; streptomycin 41.9% and 100.0%; pyrazinamide 15% and 94.8%; and ethambutol 75.0% and 98.6%, respectively. We found novel mutations encoding resistance to streptomycin (in gidB) and pyrazinamide (in kefB). Most isolates belonged to lineage 4 (80.1%) and the overall clustering rate was 11.5%. We observed lineage-specific gene variations encoding resistance to streptomycin and pyrazinamide.

CONCLUSIONS: This study highlights the clinical potential of WGS in ruling out false-positive drug resistance following phenotypic or genetic drug testing, and recommend this technology together with the WHO catalogue in designing an optimal individualized treatment regimen and preventing the development of MDR TB. Our results suggest that resistance is primarily developed through spontaneous mutations or selective pressure.

DOI: 10.1093/jacamr/dlad108
PMCID: PMC10549209
PMID: 37799267

38. Exploring and exploiting the host cell autophagy during Mycobacterium tuberculosis infection.

Eur J Clin Microbiol Infect Dis. 2023 Nov;42(11):1297-1315. doi:

10.1007/s10096-023-04663-0. Epub 2023 Sep 23.

Nagdev PK(1), Agnivesh PK(1), Roy A(1), Sau S(1), Kalia NP(2).

Tuberculosis, caused by Mycobacterium tuberculosis, is a fatal infectious disease that prevails to be the second leading cause of death from a single infectious agent despite the availability of multiple drugs for treatment. The current treatment regimen involves the combination of several drugs for 6 months that remain ineffective in completely eradicating the infection because of several drawbacks, such as the long duration of treatment and the side effects of drugs causing non-adherence of patients to the treatment regimen. Autophagy is an intracellular degradative process that eliminates pathogens at the early stages of infection. Mycobacterium tuberculosis's unique autophagy-blocking capability makes it challenging to eliminate compared to usual pathogens. The present review discusses recent advances in autophagy-inhibiting factors and mechanisms that could be exploited to identify autophagy-inducing chemotherapeutics that could be used as adjunctive therapy with the existing first-line anti-TB agent to shorten the duration of therapy and enhance cure rates from multidrug-resistant tuberculosis (MDR-TB) and extreme drug-resistant tuberculosis (XDR-TB).

DOI: 10.1007/s10096-023-04663-0
PMID: 37740791

39. Targeting Mycobacterium tuberculosis iron-scavenging tools: a recent update on siderophores inhibitors.

RSC Med Chem. 2023 Sep 6;14(10):1885-1913. doi: 10.1039/d3md00201b. eCollection 2023 Oct 18.

Kumar G(1), Adhikrao PA(1).

Among the various bacterial infections, tuberculosis (TB) remains a life-threatening infectious disease responsible as the most significant cause of mortality and morbidity worldwide. The co-infection of human immunodeficiency virus (HIV) in association with TB burdens the healthcare system substantially. Notably, M.tb possesses defence against most antitubercular antibiotic drugs, and the efficacy of existing frontline anti-TB drugs is waning. Also, new and recurring cases of TB from resistant bacteria such as multidrug-resistant TB (MDR), extensively drug-resistant TB (XDR), and totally drug-resistant TB (TDR) strains are increasing. Hence, TB begs the scientific community to explore the

new therapeutic class of compounds with their novel mechanism. M.tb requires iron from host cells to sustain, grow, and carry out several biological processes. M.tb has developed strategic methods of acquiring iron from the surrounding environment. In this communication, we discuss an overview of M.tb iron-scavenging tools. Also, we have summarized recently identified MbtA and MbtI inhibitors, which prevent M.tb from scavenging iron. These iron-scavenging tool inhibitors have the potential to be developed as anti-TB agents/drugs.

DOI: 10.1039/d3md00201b
PMCID: PMC10583813
PMID: 37859726

Conflict of interest statement: There is no conflict of interest to declare.

40. Model-based Dose Optimization Framework for Bedaquiline, Pretomanid, and Linezolid for the Treatment of Drug-Resistant Tuberculosis.

Br J Clin Pharmacol. 2023 Oct 10. doi: 10.1111/bcp.15925. Online ahead of print.

Mehta K(1), Guo T(1), Van der Graaf PH(1)(2), van Hasselt JGC(1).

AIM: Bedaquiline, pretomanid, and linezolid combination (BPaL) treatment against Mycobacterium tuberculosis is promising yet safety and adherence concerns exist that motivates exploration of alternative dosing regimens. We developed a mechanistic modeling framework to compare the efficacy of the current and alternative BPaL treatment strategies.

METHODS: Pharmacodynamic models for each drug in the BPaL combination treatment were developed using in vitro time-kill data. These models were combined with pharmacokinetic models, incorporating bodyweight, lesion volume, site-of-action distribution, bacterial susceptibility, and pharmacodynamic interactions to assemble the framework. The model was qualified by comparing the simulations against the observed clinical data. Simulations were performed evaluating bedaquiline and linezolid approved (bedaquiline 400mg once daily (QD) 14-days followed by 200mg three times a week, linezolid 1200mg QD) and alternative dosing regimens (bedaquiline 200mg QD, linezolid 600mg QD).

RESULTS: The framework adequately described the observed anti-bacterial activity data in patients following monotherapy for each drug and approved BPaL dosing. The simulations suggested a minor difference in median time to colony forming units (CFU)-clearance state with the bedaquiline alternative compared to the approved dosing and the linezolid alternative compared to the approved dosing.

Median time to non-replicating-clearance state was predicted to be 15-days from the CFU-clearance state.

CONCLUSION: The model-based simulations suggested that comparable efficacy can be achieved using alternative bedaquiline and linezolid dosing, which may improve safety and adherence in drug-resistant tuberculosis patients. The framework can be utilized to evaluate treatment optimization approaches, including dosing regimen and duration of treatment predictions to eradicate both replicating- and non-replicating bacteria from lung and lesions.

DOI: 10.1111/bcp.15925
PMID: 37817504

41. Microbial glycosylation of antitubercular agent chlorflavonin.

J Biosci Bioeng. 2023 Nov;136(5):366-373. doi: 10.1016/j.jbiosc.2023.09.005. Epub 2023 Sep 23.

Ren J(1), Zhan J(2).

Flavonoids have shown health-benefiting properties, such as antioxidative and anti-inflammatory activities, and are commonly used as nutraceuticals and pharmaceuticals. Although flavonoids are predominantly identified from plants, several filamentous fungal species have also been reported to produce bioactive flavonoids, including chlorflavonin from Aspergillus candidus, a novel halogenated flavonoid with potent antifungal and antitubercular (anti-TB) activities. Unfortunately, the low water-solubility of this molecule may hinder its bioavailability. Glycosylation is an effective method to enhance the polarity of natural products and alter their physicochemical properties. This work focuses on the development of novel water-soluble chlorflavonin derivatives to combat the threat of drug-resistant tuberculosis. In this study, we first increased the production titer of chlorflavonin in A. candidus NRRL 5214 by optimizing the fermentation and purification processes. Next, chlorflavonin-5-O-β-d-glucuronopyranoside (1) and chlorflavonin-7-O-4″-O-methyl-β-d-glucopyranoside (2) were produced from chlorflavonin using Streptomyces chromofuscus ATCC 49982 and Beauveria bassiana ATCC 7159, respectively. Compared to chlorflavonin (4.38 ± 0.54 mg/L in water), the water solubility of the two new glycosides was determined to be 117.86 ± 4.81 mg/L (1) and 124.34 ± 9.13 mg/L (2), respectively. This study provides a promising method to create water-soluble glycosides of chlorflavonin for the development of novel anti-TB drugs.

DOI: 10.1016/j.jbiosc.2023.09.005
PMID: 37743150

42. The effect of anti-tuberculosis drug pharmacokinetics on QTc prolongation.

Int J Antimicrob Agents. 2023 Oct;62(4):106939. doi: 10.1016/j.ijantimicag.2023.106939. Epub 2023 Jul 29.

Jin Y(1), Benkeser D(1), Kipiani M(2), Maranchick NF(3), Mikiashvili L(2), Barbakadze K(2), Avaliani Z(2), Alghamdi WA(4), Alshaer MH(3), Peloquin CA(3), Blumberg HM(5), Kempker RR(6).

BACKGROUND: Implementation of newer anti-tuberculosis (TB) drugs may prolong the QT interval, increasing the risk of arrythmias and sudden cardiac death. The potential for cardiac adverse events has prompted recommendations for frequent cardiac monitoring during treatment. However, unknowns remain, including the association between drug concentrations and QT interval.

METHODS: An observational prospective cohort study design was used. Patients undergoing treatment for drug-resistant TB in Georgia were assessed. Serial blood samples were collected at 4-6 weeks for pharmacokinetics. Electrocardiograms were recommended to be performed monthly. A generalized estimating equation spline model was used to investigate (1) the effect difference between bedaquiline and delamanid, (2) the cumulative effect of number of anti-TB drugs, and (3) the relationship between serum drug concentrations on QTc interval.

RESULTS: Among 94 patients receiving either bedaquiline (n = 64) or delamanid (n = 30)-based treatment, most were male (82%), and the mean age was 39 years. The mean maximum QTc increase during the first six months was 37.5 ms (IQR: 17.8-56.8). Bedaquiline- and delamanid-based regimens displayed similar increased mean QTc change from baseline during drug administration (P = 0.12). Increasing number of anti-TB drugs was associated with an increased QTc (P = 0.01), but participants trended back towards baseline after drug discontinuation (P = 0.25). A significant association between AUC, Cmin, Cmax, and increased QTc interval was found for bedaquiline (months 1-6) and levofloxacin (months 1-12).

CONCLUSION: Bedaquiline- and delamanid-based regimens and increasing number of QT prolonging agents led to modest increases in the QTc interval with minimal clinical effect.

DOI: 10.1016/j.ijantimicag.2023.106939
PMCID: PMC10538394
PMID: 37517627 [Indexed for MEDLINE]

Conflict of interest statement: Competing Interests: None

43. Impact of Mycobacterium tuberculosis strain type on multidrug-resistant tuberculosis severity, Republic of Moldova.

J Infect. 2023 Oct 10:S0163-4453(23)00532-7. doi: 10.1016/j.jinf.2023.10.001. Online ahead of print.

Chesov E(1), Chesov D(2), Reimann M(3), Dreyer V(4), Utpatel C(4), Gröschel MI(5), Ciobanu N(6), Crudu V(6), Lange C(7), Heyckendorf J(8), Merker M(9).

DOI: 10.1016/j.jinf.2023.10.001
PMID: 37827458

Conflict of interest statement: Declaration of Competing Interest CL is supported by the German Center for Infection Research (DZIF) under grant TTU 02.709. The other authors declare no conflict of interests.

44. Discovery, Synthesis, and Optimization of 1,2,4-Triazolyl Pyridines Targeting Mycobacterium tuberculosis.

ACS Infect Dis. 2023 Oct 3. doi: 10.1021/acsinfecdis.3c00341. Online ahead of print.

Berida T(1), McKee SR(2), Chatterjee S(1), Manning DL(1), Li W(3), Pandey P(4), Tripathi SK(4), Mreyoud Y(2), Smirnov A(2), Doerksen RJ(1), Jackson M(3), Ducho C(5), Stallings CL(2), Roy S(1).

The rise in multidrug resistant tuberculosis cases underscores the urgent need to develop new treatment strategies for tuberculosis. Herein, we report the discovery and synthesis of a new series of compounds containing a 3-thio-1,2,4-triazole moiety that show inhibition of Mycobacterium tuberculosis (Mtb) growth and survival. Structure-activity relationship studies led us to identify several potent analogs displaying low micromolar to nanomolar inhibitory activity, specifically against Mtb. The potent analogs demonstrated no cytotoxicity in mammalian cells at over 100 times the effective concentration

required in Mtb and were bactericidal against Mtb during infection of macrophages. In the exploratory ADME investigations, we observed suboptimal ADME characteristics, which prompted us to identify potential metabolic liabilities for further optimization. Our preliminary investigations into the mechanism of action suggest that this series is not engaging the promiscuous targets that arise from many phenotypic screens. We selected for resistant mutants with the nanomolar potent nitro-containing compound 20 and identified resistant isolates with mutations in genes required for coenzyme F420 biosynthesis and the nitroreductase Ddn. This suggests that the aromatic nitro-1,2,4-triazolyl pyridines are activated by F420-dependent Ddn activity, similar to the nitro-containing TB drug pretomanid. We were able to circumvent the requirement for F420-dependent Ddn activity using compounds that contained non-nitro groups, identifying a key feature to be modified to avoid this predominant resistance mechanism. These studies provide the foundation for the development of a new class of 1,2,4-triazole compounds for the treatment of tuberculosis.

DOI: 10.1021/acsinfecdis.3c00341
PMID: 37788674

45. Protein binding investigation of first-line and second-line antituberculosis drugs.

Int J Antimicrob Agents. 2023 Oct 12:106999. doi: 10.1016/j.ijantimicag.2023.106999. Online ahead of print.

Fage D(1), Aalhoul F(2), Cotton F(3).

Data about antituberculosis drugs binding are incomplete for first-line drugs and lacking for second-line drugs that are used extensively for multi-drug resistant tuberculosis (levofloxacin, linezolid and moxifloxacin). Thus, the main purposes of this study were first to investigate thoroughly the relation between the carrier-proteins level and the drug binding and second to investigate the feasibility of predicting the free drug concentrations by the means of in vitro and in vivo results. In vitro experiments mimicked real-case samples by spiking drugs combinations from the clinical practice. We measured a median in vivo protein binding of 1.5% for ethambutol, 9.7% for isoniazid, 0.7% for pyrazinamide and 88.2% for rifampicin; and a median in vitro protein binding of 26.2% for levofloxacin, 12.8% for linezolid and 46.3% for moxifloxacin. The albumin concentration had a moderate impact on the moxifloxacin binding and a strong impact on the levofloxacin, linezolid and rifampicin binding (below values of 30 g/L). The determination of the free drug concentration seems to have few interests for ethambutol, isoniazid, moxifloxacin and pyrazinamide, a limited interest for linezolid because of its low binding and a major interest for rifampicin in hypoalbuminemia TB patients and for levofloxacin because their

total concentration was an inaccurate reflection of the free concentration. The free concentration predicted by mathematical model was suitable for levofloxacin and linezolid, unlike for rifampicin, where the real free concentration should be measured. Further investigations should be carried out to investigate the benefit of the free concentration for levofloxacin, linezolid and rifampicin mainly in the critical period of active tuberculosis associated to hypoalbuminemia.

DOI: 10.1016/j.ijantimicag.2023.106999
PMID: 37838149

46. In vitro bioevaluation and docking study of dihydrosphingosine and ethambutol analogues against sensitive and multi-drug resistant Mycobacterium tuberculosis.

Eur J Med Chem. 2023 Oct 5;258:115579. doi: 10.1016/j.ejmech.2023.115579. Epub 2023 Jun 19.

Linhares LA(1), Dos Santos Peixoto A(2), Correia de Sousa LA(2), Lucena Laet JP(2), da Silva Santos AC(3), Alves Pereira VR(3), Carneiro Neves MM(4), Ferreira LFGR(5), Hernandes MZ(5), de la Vega J(6), Pereira-Neves A(3), San Feliciano A(7), Olmo ED(6), Schindler HC(2), Montenegro LML(8).

Tuberculosis remains a major public health problem and one of the top ten causes of death worldwide. The alarming increase in multidrug-resistant and extensively resistant variants (MDR, pre-XDR, and XDR) makes the disease more difficult to treat and control. New drugs that act against MDR/XDR strains are needed for programs to contain this major epidemic. The present study aimed to evaluate new compounds related to dihydro-sphingosine and ethambutol against sensitive and pre-XDR Mycobacterium strains, as well as to characterize the pharmacological activity through in vitro and in silico approaches in mmpL3 protein. Of the 48 compounds analyzed, 11 demonstrated good to moderate activity on sensitive and MDR Mycobacterium tuberculosis (Mtb), with a Minimum Inhibitory Concentration (MIC) ranging from 1.5 to 8 μM. They presented 2 to 14 times greater potency of activity when compared to ethambutol in pre-XDR strain, and demonstrated a selectivity index varying between 2.21 and 82.17. The substance 12b when combined with rifampicin, showed a synergistic effect (FICI = 0.5) on sensitive and MDR Mtb. It has also been shown to have a concentration-dependent intracellular bactericidal effect, and a time-dependent bactericidal effect in M. smegmatis and pre-XDR M. tuberculosis. The binding mode of the compounds in its cavity was identified through molecular docking and using a predicted structural model of mmpL3. Finally, we observed by transmission electron microscopy the induction of damage to the cell wall integrity of M. tuberculosis

treated with the substance 12b. With these findings, we demonstrate the potential of a 2-aminoalkanol derivative to be a prototype substance and candidate for further optimization of molecular structure and anti-tubercular activity in preclinical studies.

DOI: 10.1016/j.ejmech.2023.115579
PMID: 37399709 [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.

47. Global efforts to improve tuberculosis drug availability.

Lancet Respir Med. 2023 Oct;11(10):868. doi: 10.1016/S2213-2600(23)00302-8. Epub 2023 Aug 11.

Burki T.

DOI: 10.1016/S2213-2600(23)00302-8
PMID: 37579771 [Indexed for MEDLINE]

48. Design, synthesis and antitubercular activity of novel N-(amino)piperazinyl benzothiazinones with improved safety.

Eur J Med Chem. 2023 Oct 5;258:115545. doi: 10.1016/j.ejmech.2023.115545. Epub 2023 Jun 5.

Wang A(1), Du N(1), Song H(1), Zhang Y(2), Zhong X(1), Wu J(1), Xue T(2), Liu M(3), Wang B(4), Lv K(5), Lu Y(6).

Tuberculosis (TB), caused by Mycobacterium tuberculosis (MTB) remains a major global health problem and new therapeutic antitubercular agents are urgent needed. Among the novel antituberculosis drugs in the pipeline, Benzothiazinones (BTZs) are among the most potent antituberculosis agents against both drug-susceptible and multidrug-resistant (MDR) tuberculosis. Our group has focused on structural modifications of the side chain at C-2 position of the BTZ core and WAP-2101/2102 with excellent in vitro activity were discovered in our lab. However, the severe in vivo toxicity was observed during subsequent acute toxicity evaluation. Herein, a series of novel N-(amino)piperazinyl benzothiazinone derivatives were designed and synthesized as new anti-TB agents

to reduce the in vivo toxicity. Our results show that majority of them exhibit the same potent or comparable activity against both MTB H37Rv and MDR-MTB strains (MIC: 4.00 - <1 ng/mL) as PBTZ169. Especially, compound 2c with low cardiac toxicity, low cell cytotoxicity and acceptable oral pharmacokinetic (PK) profiles have low acute toxicity in mice (LD50 > 500 mg/kg), suggesting it may serve as a promising lead compound for further antitubercular drug discovery.

DOI: 10.1016/j.ejmech.2023.115545
PMID: 37300914 [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.

49. Implementation of Bedaquiline, Pretomanid, and Linezolid in the United States: Experience Using a Novel All-Oral Treatment Regimen for Treatment of Rifampin-Resistant or Rifampin-Intolerant Tuberculosis Disease.

Clin Infect Dis. 2023 Oct 5;77(7):1053-1062. doi: 10.1093/cid/ciad312.

Haley CA(1)(2), Schechter MC(3)(4), Ashkin D(1), Peloquin CA(5), Peter Cegielski J(6), Andrino BB(7), Burgos M(8)(9)(10), Caloia LA(11)(12), Chen L(13), Colon-Semidey A(14), DeSilva MB(15)(16), Dhanireddy S(17), Dorman SE(18)(19), Dworkin FF(20), Hammond-Epstein H(21), Easton AV(20), Gaensbauer JT(22), Ghassemieh B(23)(24), Gomez ME(21), Horne D(25), Jasuja S(26), Jones BA(27), Kaplan LJ(28), Khan AE(29), Kracen E(23)(24), Labuda S(30), Landers KM(31), Lardizabal AA(32), Lasley MT(21), Letzer DM(33), Lopes VK(34)(35), Lubelchek RJ(26)(36)(37), Patricia Macias C(38)(39), Mihalyov A(11), Misch EA(40), Murray JA(41)(42), Narita M(23)(24), Nilsen DM(20), Ninneman MJ(43), Ogawa L(15), Oladele A(44), Overman M(19), Ray SM(3)(4), Ritger KA(45), Rowlinson MC(27)(46), Sabuwala N(47), Schiller TM(48), Schwartz LE(49), Spitters C(17)(50)(51), Thomson DB(52), Tresgallo RR(53), Valois P(27), Goswami ND(54); BPaL Implementation Group.

Collaborators: Agraz-Lara R, Ahmed A, Alvarez A, Armitage L, Barry P, Belknap R, Bernardo J, Bravo M, Brode S, Burden E, Burzynski J, Caplan-Shaw C, Castro K, Chorba T, Connors W, Cook V, Cruz A, Daley C, Dasgupta S, Dhingra S, Dobbs T, Elmore E, Erwin F, Escuyer V, Fiske C, Gadkowski B, Henestroza G, Higashi J, Katrak S, Keh C, Khalil A, Kigonya L, Lauzardo M, Morris S, Munsiff S, Nabity S, Oxtoby M, Patrawalla A, Phillips A, Raftery A, Reed C, Rock B, Russo K, Sahini H, Saleeb P, Santos R, Seaworth B, Shaw-KaiKai J, Starke J, Stout J,

Stubblefield W, Temesgen Z, Thomas K, Tornheim J, Upton C, Urbine D, Wang SH, Warkentin J, Webb R, Wilson J, Wortham J, Yu AS, Altman C, Hafiz I, Prabhakar D, Bowler W.

Comment in
Clin Infect Dis. 2023 Oct 5;77(7):1063-1064.

BACKGROUND: Rifampin-resistant tuberculosis is a leading cause of morbidity worldwide; only one-third of persons start treatment, and outcomes are often inadequate. Several trials demonstrate 90% efficacy using an all-oral, 6-month regimen of bedaquiline, pretomanid, and linezolid (BPaL), but significant toxicity occurred using 1200-mg linezolid. After US Food and Drug Administration approval in 2019, some US clinicians rapidly implemented BPaL using an initial 600-mg linezolid dose adjusted by serum drug concentrations and clinical monitoring.

METHODS: Data from US patients treated with BPaL between 14 October 2019 and 30 April 2022 were compiled and analyzed by the BPaL Implementation Group (BIG), including baseline examination and laboratory, electrocardiographic, and clinical monitoring throughout treatment and follow-up. Linezolid dosing and clinical management was provider driven, and most patients had linezolid adjusted by therapeutic drug monitoring.

RESULTS: Of 70 patients starting BPaL, 2 changed to rifampin-based therapy, 68 (97.1%) completed BPaL, and 2 of the 68 (2.9%) experienced relapse after completion. Using an initial 600-mg linezolid dose daily adjusted by therapeutic drug monitoring and careful clinical and laboratory monitoring for adverse effects, supportive care, and expert consultation throughout BPaL treatment, 3 patients (4.4%) with hematologic toxicity and 4 (5.9%) with neurotoxicity required a change in linezolid dose or frequency. The median BPaL duration was 6 months.

CONCLUSIONS: BPaL has transformed treatment for rifampin-resistant or intolerant tuberculosis. In this cohort, effective treatment required less than half the duration recommended in 2019 US guidelines for drug-resistant tuberculosis. Use of individualized linezolid dosing and monitoring likely enhanced safety and treatment completion. The BIG cohort demonstrates that early implementation of new tuberculosis treatments in the United States is feasible.

DOI: 10.1093/cid/ciad312

PMID: 37249079 [Indexed for MEDLINE]

Conflict of interest statement: Potential conflicts of interest. C. A. H. reports honoraria from the Infectious Diseases Society of America for an IDWeek 2022 presentation, travel support from the University of Employer, and Pfizer stock ownership. M. C. S. reports grants from the National Institute of Minority Health and Health Disparities (R21MD017943-01; Neighborhood transportation vulnerability and geographic patterns of diabetes-related limb loss) and the American Diabetes Association (Diabetic Ulcer Computational Sensing System), paid to the institution, and payment from the Society for Advancement in Wound Care for speaking at the 2023 spring meeting. D. A. reports a grant from the Centers for Disease Control and Prevention (CDC) as the primary investigator of TB Centers of Excellence, travel support from the CDC, and participation in the CDC's Tuberculosis Trials Consortium data and safety monitoring board. L. C. reports grants from USAID (federal award to institution for global research capacity building) and the California Department of Public Health (training award to institution for pandemic response); an unpaid position as president of the Executive Leadership Board for the North American Region Union Against Tuberculosis and Lung Diseases; and an unpaid position on the coordinating board of STOP TB USA. M. B. D reports institutional contracts with the CDC and Westat. A. V. E. reports travel support for meetings from the CDC. K. A. R. reports grants and travel support from the CDC’s Division of TB Elimination and a position as the liaison for the National Association of County and City Health Officials to the Advisory Committee for the Elimination of Tuberculosis. M. C. R. reports travel support for meeting from Association of Public Health Laboratories (APHL) and positions as chair of the APHL Infectious Diseases Committee and member of the APHL Tuberculosis Subcommittee and the College of American Pathologists Microbiology Committee. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

50. Australian recommendations for the management of drug-resistant tuberculosis, 2023.

Commun Dis Intell (2018). 2023 Oct 19;47. doi: 10.33321/cdi.2023.47.48.

Stapledon R(1), Donnan EJ(2), National Tuberculosis Advisory Committee Ntac(3).

DOI: 10.33321/cdi.2023.47.48
PMID: 37857558 [Indexed for MEDLINE]

51. [A case of giant pleural tuberculoma].

Zhonghua Jie He He Hu Xi Za Zhi. 2023 Oct 12;46(10):1008-1010. doi: 10.3760/cma.j.cn112147-20230415-00177.
[Article in Chinese; Abstract available in Chinese from the publisher]

Li YQ(1), Sun KK(2), Ma XH(1), Gao ZC(1).

Author information:
(1)Department of Respiratory and Critical Care Medicine, Peking University People's Hospital, Beijing 100044, China.
(2)Department of Radiology, Peking University People's Hospital, Beijing 100044, China Ma Xiaohong is working on the Department of Respiratory Medicine, Shuocheng District People's Hospital, Shuozhou 036800, China.

We retrospectively analyzed a rare case of giant pleural tuberculoma. The patient was a female, 62 years old, admitted to hospital for intermittent fever and hemoptysis. The CT scan of the chest and abdomen showed a mass in the right thoracic cavity, and the uneven surface of the bilateral fallopian tubes. Routine blood tests showed a decrease in platelets, white blood cells, and hemoglobin. The mass in the chest was finally confirmed as a tuberculoma by biopsy. The patient was diagnosed with tuberculosis more than 9 years ago and had been treated with anti-tuberculosis drugs for more than 9 years, which caused damage to the liver, bone marrow and other organs, and led to the drug-resistant tuberculosis, making diagnosis and treatment more complex.

DOI: 10.3760/cma.j.cn112147-20230415-00177
PMID: 37752043 [Indexed for MEDLINE]

52. An Overview of Various Rifampicin Analogs against Mycobacterium tuberculosis and their Drug Interactions.

Med Chem. 2023 Oct 5. doi: 10.2174/0115734064260853230926080134. Online ahead of print.

Asif M(1), Qusty NF(2), Alghamdi S(2).

The success of the TB control program is hampered by the major issue of drug-resistant tuberculosis (DR-TB). The situation has undoubtedly been made more difficult by the widespread and multidrug-resistant (XDR) strains of TB. The modification of existing anti-TB medications to produce derivatives that can function on resistant TB bacilli is one of the potential techniques to overcome drug resistance affordably and straightforwardly. In comparison to novel pharmaceuticals for drug research and progress, these may have a better half-life and greater bioavailability, be more efficient, and serve as inexpensive alternatives. Mycobacterium tuberculosis, which is drugsusceptible

or drug-resistant, is effectively treated by several already prescribed medications and their derivatives. Due to this, the current review attempts to give a brief overview of the rifampicin derivatives that can overcome the parent drug's resistance and could, hence, act as useful substitutes. It has been found that one-third of the global population is affected by M. tuberculosis. The most common cause of infection-related death can range from latent TB to TB illness. Antibiotics in the rifamycin class, including rifampicin or rifampin (RIF), rifapentine (RPT), and others, have a special sterilizing effect on M. tuberculosis. We examine research focused on evaluating the safety, effectiveness, pharmacokinetics, pharmacodynamics, risk of medication interactions, and other characteristics of RIF analogs. Drug interactions are especially difficult with RIF because it must be taken every day for four months to treat latent TB infection. RIF continues to be the gold standard of treatment for drug-sensitive TB illness. RIF's safety profile is well known, and the two medicines' adverse reactions have varying degrees of frequency. The authorized once-weekly RPT regimen is insufficient, but greater dosages of either medication may reduce the amount of time needed to treat TB effectively.

DOI: 10.2174/0115734064260853230926080134
PMID: 37855280

53. Rapid detection of fluoroquinolone resistance in Mycobacterium tuberculosis using a novel multienzyme isothermal rapid assay.

J Antibiot (Tokyo). 2023 Oct;76(10):598-602. doi: 10.1038/s41429-023-00639-6. Epub 2023 Jul 4.

Li MC(#)(1), Lu Y(#)(2), Liu HC(#)(1), Lin SQ(3), Qian C(4), Nan XT(1), Li GL(1), Zhao XQ(1), Wan KL(1), Zhao LL(5).

Simple, rapid, and accurate detection of Fluoroquinolone (FQ) resistance is essential for early initiation of appropriate anti-tuberculosis treatment regimen among rifampicin-resistant tuberculosis (RR-TB). In this study, we developed a new assay, which combines multienzyme isothermal rapid amplification and a lateral flow strip (MIRA-LF), to identify the mutations on codons 90 and 94 of gyrA for detecting levofloxacin (LFX) resistance. Compared to conventional phenotypic drug susceptibility testing, the new assay detected fluoroquinolone resistance with a sensitivity, specificity, and accuracy of 92.4%, 98.5%, and 96.5%, respectively. Thus, these characteristics of the newly developed MIRA-LF assay make it particularly useful and accurate for detecting FQ resistance in Mycobacterium tuberculosis in resource-limited condition.

DOI: 10.1038/s41429-023-00639-6
PMID: 37402884 [Indexed for MEDLINE]

54. Combination of MCL-1 and BCL-2 inhibitors is a promising approach for a host-directed therapy for tuberculosis.

Biomed Pharmacother. 2023 Oct 19;168:115738. doi: 10.1016/j.biopha.2023.115738. Online ahead of print.

Arnett E(1), Pahari S(2), Leopold Wager CM(2), Hernandez E(2), Bonifacio JR(2), Lumbreras M(2), Renshaw C(2), Montoya MJ(2), Opferman JT(3), Schlesinger LS(4).

Tuberculosis (TB) accounts for 1.6 million deaths annually and over 25% of deaths due to antimicrobial resistance. Mycobacterium tuberculosis (M.tb) drives MCL-1 expression (family member of anti-apoptotic BCL-2 proteins) to limit apoptosis and grow intracellularly in human macrophages. The feasibility of re-purposing specific MCL-1 and BCL-2 inhibitors to limit M.tb growth, using inhibitors that are in clinical trials and FDA-approved for cancer treatment has not be tested previously. We show that specifically inhibiting MCL-1 and BCL-2 induces apoptosis of M.tb-infected macrophages, and markedly reduces M.tb growth in human and murine macrophages, and in a pre-clinical model of human granulomas. MCL-1 and BCL-2 inhibitors limit growth of drug resistant and susceptible M.tb in macrophages and act in additive fashion with the antibiotics isoniazid and rifampicin. This exciting work uncovers targeting the intrinsic apoptosis pathway as a promising approach for TB host-directed therapy. Since safety and activity studies are underway in cancer clinics for MCL-1 and BCL-2 inhibitors, we expect that re-purposing them for TB treatment should translate more readily and rapidly to the clinic. Thus, the work supports further development of this host-directed therapy approach to augment current TB treatment.

DOI: 10.1016/j.biopha.2023.115738
PMID: 37864894

Conflict of interest statement: Declaration of Competing Interest The following patents have been submitted: Provisional patent number: 63/069,086, international patent number: PCT/US2021/047074.

55. Transmission dynamics and phylogeography of Mycobacterium tuberculosis in China based on whole-genome phylogenetic analysis.

Int J Infect Dis. 2023 Oct 18:S1201-9712(23)00752-X. doi: 10.1016/j.ijid.2023.10.015. Online ahead of print.

Li YF(1), Yang Y(2), Kong XL(3), Song WM(4), Li YM(5), Li YY(5), Fang WW(4), Yang JY(4), Men D(6), Yu CB(7), Yang GR(8), Han WG(8), Liu WY(8), Yan K(8), Li HC(4), Liu Y(9).

OBJECTIVE: To describe the lineage-specific transmissibility and epidemiological migration of Mycobacterium tuberculosis in China.

METHODS: We curated a large set of whole genome sequences from 3204 M. tuberculosis isolates, including thousands of newly sequenced genomes, and applied a series of metrics to compare the transmissibility of M. tuberculosis strains between lineages and sublineages. The countrywide transmission patterns of major lineages were explored.

RESULTS: We found that lineage 2 (L2) was the most prevalent lineage in China (85.7%), with the major sublineage 2.2.1 (80.9%), followed by lineage 4 (L4) (13.8%), which comprises major sublineages 4.2 (1.5%), 4.4 (6.2%) and 4.5 (5.8%). We showed evidence for frequent cross-regional spread and large cluster formation of L2.2.1 strains, whereas L4 strains were relatively geographically restricted in China. Next, we applied a series of genomic indices to evaluate M. tuberculosis strain transmissibility and uncovered higher transmissibility of L2.2.1 compared with the L2.2.2 and L4 sublineages. Phylogeographic analysis showed that southern, eastern, and northern China were highly connected regions for countrywide L2.2.1 strain spread.

CONCLUSIONS: The present study provides insights into the different transmission and migration patterns of the major M. tuberculosis lineages in China and highlights that transmissible L2.2.1 is a threat to tuberculosis control.

DOI: 10.1016/j.ijid.2023.10.015
PMID: 37863309

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