Open Access Articles

3. **Characteristics of Previous Tuberculosis Treatment History in Patients with Treatment Failure and the Impact on Acquired Drug-Resistant Tuberculosis.**

Antibiotics (Basel). 2023 Mar 16;12(3):598. doi: 10.3390/antibiotics12030598.

Soedarsono S(1)(2), Mertaniasih NM(3)(4), Kusmiati T(1)(4), Permatasari A(1)(4), Ilahi WK(5), Anggraeni AT(5).

Tuberculosis (TB) treatment failure is a health burden, as the patient remains a source of infection and may lead to the development of multi-drug resistance (MDR). Information from cases of treatment failure that develop into MDR, which is related to a history of previous TB treatment, in accordance with the pharmacokinetic aspect, is one important thing to prevent TB treatment failure and to prevent drug resistance. This was an observational descriptive study in an acquired MDR-TB patient who had a prior history of treatment failure. A structured questionnaire was used to collect information. The questionnaire consisted of a focus on the use of TB drug formulas during the treatment period, as well as when and how to take them. This study included 171 acquired MDR-TB patients from treatment failure cases. An amount of 64 patients received the separated TB drug, and 107 patients received the fixed dose combination (FDC) TB drug. An amount of 21 (32.8%) patients receiving separated TB drug and six (5.6%) patients receiving FDC TB drug took their drug in divided doses. In addition, three (4.7%) patients receiving separated TB drug and eight (7.5%) patients receiving FDC TB drug took their drug with food. An amount of 132 out of 171 (77.2%) patients had a history of incorrect treatment that developed into MDR-TB. Education on how to take the correct medication, both the separate version and the FDC TB drug, according to the pharmacokinetic aspect, is important before starting TB treatment.

DOI: 10.3390/antibiotics12030598
PMCID: PMC10044547
PMID: 36978465

Conflict of interest statement: The author reports no conflict of interest in this work.

4. **Tuberculosis: Pathogenesis, Current Treatment Regimens and New Drug Targets.**

Int J Mol Sci. 2023 Mar 8;24(6):5202. doi: 10.3390/ijms24065202.

Alsayed SSR(1), Gunosewoyo H(1)(2).

Mycobacterium tuberculosis (M. tb), the causative agent of TB, is a recalcitrant pathogen that is rife around the world, latently infecting approximately a quarter of the worldwide population. The asymptomatic status of the dormant bacteria escalates to the transmissible, active form when the host's immune system becomes debilitated. The current front-line treatment regimen for drug-sensitive (DS) M. tb strains is a 6-month protocol involving four different drugs that requires stringent adherence to avoid relapse and resistance. Poverty, difficulty to access proper treatment, and lack of patient compliance contributed to the emergence of more sinister drug-resistant (DR) strains, which demand a longer duration of treatment with more toxic and more expensive drugs compared to the first-line regimen. Only three new drugs, bedaquiline (BDQ) and the two nitroimidazole derivatives delamanid (DLM) and pretomanid (PMD) were approved in the last decade for treatment of TB-the first anti-TB drugs with novel mode of actions to be introduced to the market in more than 50 years-reflecting the attrition rates in the development and approval of new anti-TB drugs. Herein, we will discuss the M. tb pathogenesis, current treatment protocols and challenges to the TB control efforts. This review also aims to highlight several small molecules that have recently been identified as promising preclinical and clinical anti-TB drug candidates that inhibit new protein targets in M. tb.

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PMCID: PMC10049048
PMID: 36982277 [Indexed for MEDLINE]

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

5. **Update of drug-resistant tuberculosis treatment guidelines: A turning point.**

Int J Infect Dis. 2023 Mar 12:S1201-9712(23)00089-9. doi: 10.1016/j.ijid.2023.03.013. Online ahead of print.

Vanino E(1), Granozzi B(2), Akkerman OW(3), Munoz-Torrico M(4), Palmieri F(5), Seaworth B(6), Tiberi S(7), Tadolini M(8).

In December 2022 World Health Organization released a new treatment for multidrug-resistant/rifampicin-resistant tuberculosis (MDR/RR-TB) guideline. The main novelty of this update is two new recommendations (i) a 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid (600 mg), and moxifloxacin (BPaLM) is recommended in place of the 9-month or longer (18-month)

regimens in MDR/RR-TB patients, now including extensive pulmonary TB and extrapulmonary TB (except TB involving central nervous system, miliary TB and osteoarticular TB); (ii) the use of the 9-month all-oral regimen rather than longer (18-months) regimen is suggested in patients with MDR/RR-TB and in whom resistance to fluoroquinolones has been excluded. Longer (18-month) treatments remain a valid option in all cases in which shorter regimens cannot be implemented due to intolerance, drug-drug interactions, extensively drug-resistant tuberculosis, extensive forms of extrapulmonary TB, or previous failure. The new guidelines represent a milestone in MDR/RR-TB treatment landscape, setting the basis for a shorter, all-oral, more acceptable, equitable, and patient-centered model for MDR/RR-TB management. However, some challenges remain to be addressed to allow full implementation of the new recommendations.

DOI: 10.1016/j.ijid.2023.03.013
PMID: 36918080

Conflict of interest statement: Declaration of competing interests Tiberi S. is an employee of GSK, all opinions are his own and not that of the company. All other 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.

6. **Patterns and trends of primary drug-resistant tuberculosis in Chongqing, China, from 2012 to 2020.**

Medicine (Baltimore). 2023 Mar 10;102(10):e33230. doi: 10.1097/MD.0000000000033230.

Zhang H(1), Yang J(2), Zhang Z(3), Hu K(4), Wu P(5), Zhang H(6), Li J(1), Li M(1), Wang X(7).

Primary drug-resistant tuberculosis (DR-TB) contributes significantly to the global TB epidemic, particularly in countries with high TB burdens. This study aimed to investigate the characteristics of primary DR-TB prevalence in Chongqing, China, from 2012 to 2020. A total of 4546 newly diagnosed and 2769 relapse TB patients admitted to the hospital from 2012 to 2020 were included. Categorical variables were compared using Pearson chi-square test or Fisher exact test, as appropriate. Logistic regression analysis was performed to determine factors associated with primary DR-TB. The rate of primary DR-TB was 24.5%, whereas that of acquired DR-TB was 67.8%. Among newly diagnosed TB cases,

the percentage of DR-TB (from 48.9 to 44.2%), mono-resistant TB (from 11.8 to 9.7%), multidrug-resistant TB (MDR-TB; from 25.3 to 6.9%), and pre-extensive drug-resistant TB (from 13.7 to 5.8%) showed a decreasing trend from 2012 to 2020. Age from 15 to 64 years was a risk factor for the development of primary DR-TB (15-44 years: adjusted odds ratio = 2.227, 95% confidence interval: 1.053-4.710; 45-64 years: adjusted odds ratio = 2.223, 95% confidence interval: 1.048-4.717). The rates of primary DR-TB (P = .041) and MDR-TB (P = .007) were significantly higher in the age group of 15 to 64 years than in the age groups of ≤14 years and ≥65 years. Noticeably, rising trends of primary DR-TB (from 0 to 27.3%) and MDR-TB (from 0 to 9.1%) in the population of ≤14 years were observed from 2012 to 2020. Although the rate of primary DR-TB showed a downward trend, a rising drug-resistance rate among some particular subgroups was still observed. Further control of primary DR-TB should focus more on TB patients aged 15 to 64 years.

DOI: 10.1097/MD.0000000000033230
PMCID: PMC9997792
PMID: 36897690 [Indexed for MEDLINE]

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

7. **The Evolution and Transmission Dynamics of Multidrug-Resistant Tuberculosis in an Isolated High-Plateau Population of Tibet, China.**

Microbiol Spectr. 2023 Mar 13:e0399122. doi: 10.1128/spectrum.03991-22. Online ahead of print.

Jiang Q(1), Liu HC(2), Liu QY(3), Phelan JE(4), Tao FX(1), Zhao XQ(2), Wang J(5), Glynn JR(6), Takiff HE(7), Clark TG(4)(6), Wan KL(2), Gao Q(8).

On the Tibetan Plateau, most tuberculosis is caused by indigenous Mycobacterium tuberculosis strains with a monophyletic structure and high-level drug resistance. This study investigated the emergence, evolution, and transmission dynamics of multidrug-resistant tuberculosis (MDR-TB) in Tibet. The whole-genome sequences of 576 clinical strains from Tibet were analyzed with the TB-profiler tool to identify drug-resistance mutations. The evolution of the drug resistance was then inferred based on maximum-likelihood phylogeny and dated trees that traced the serial acquisition of mutations conferring resistance to different drugs. Among the 576 clinical M. tuberculosis strains, 346 (60.1%) carried at least 1 resistance-conferring mutation and 231 (40.1%) were MDR-TB. Using a

pairwise distance of 50 single nucleotide polymorphisms (SNPs), most strains (89.9%, 518/576) were phylogenetically separated into 50 long-term transmission clusters. Eleven large drug-resistant clusters contained 76.1% (176/231) of the local multidrug-resistant strains. A total of 85.2% of the isoniazid-resistant strains were highly transmitted with an average of 6.6 cases per cluster, of which most shared the mutation KatG Ser315Thr. A lower proportion (71.6%) of multidrug-resistant strains were transmitted, with an average cluster size of 2.9 cases. The isoniazid-resistant clusters appear to have undergone substantial bacterial population growth in the 1970s to 1990s and then subsequently accumulated multiple rifampicin-resistance mutations and caused the current local MDR-TB burden. These findings highlight the importance of detecting and curing isoniazid-resistant strains to prevent the emergence of endemic MDR-TB. IMPORTANCE Emerging isoniazid resistance in the 1970s allowed M. tuberculosis strains to spread and form into large multidrug-resistant tuberculosis clusters in the isolated plateau of Tibet, China. The epidemic was driven by the high risk of transmission as well as the potential of acquiring further drug resistance from isoniazid-resistant strains. Eleven large drug-resistant clusters consisted of the majority of local multidrug-resistant cases. Among the clusters, isoniazid resistance overwhelmingly evolved before all the other resistance types. A large bacterial population growth of isoniazid-resistant clusters occurred between 1970s and 1990s, which subsequently accumulated rifampicin-resistance-conferring mutations in parallel and accounted for the local multidrug-resistant tuberculosis burden. The results of our study indicate that it may be possible to restrict MDR-TB evolution and dissemination by prioritizing screening for isoniazid (INH)-resistant TB strains before they become MDR-TB and by adopting measures that can limit their transmission.

DOI: 10.1128/spectrum.03991-22
PMID: 36912683

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

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

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

Tuberculosis (TB) is among the most common cause of serositis. There are many uncertainties in diagnostic and therapeutic approach to serous membranes tuberculosis. Our aim in the present review is to discuss the regional facilities for timely diagnosis, rapid decision-making and appropriate treatment regarding to serous membranes tuberculosis; with emphasis on situation in Iran. A comprehensive literature searches about the status of serous membranes

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

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

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

9. **Strain diversity and gene mutations associated with presumptive multidrug-resistant Mycobacterium tuberculosis complex isolates in Northwest Ethiopia.**

J Glob Antimicrob Resist. 2023 Mar;32:167-175. doi: 10.1016/j.jgar.2022.11.012. Epub 2022 Dec 5.

Ejo M(1), Torrea G(2), Diro E(3), Abebe A(4), Kassa M(4), Girma Y(4), Tesfa E(5), Ejigu K(6), Uwizeye C(2), Gehre F(7), de Jong BC(2), Rigouts L(8).

OBJECTIVES: In this study, we assessed the genetic diversity and gene mutations

that confer resistance to rifampicin (RIF), isoniazid (INH), fluoroquinolone (FQ), and second-line injectable (SLI) drugs in RIF-resistant (RR)/multidrug-resistant tuberculosis (MDR-TB) isolates in Northwest Ethiopia.
METHODS: Spoligotyping was used to assign isolates to TB lineages (Ls), and Hain line probe assays were used to detect resistance to RIF, INH, and FQs, and SLIs.
RESULTS: Among 130 analyzed strains, 68.5% were RR, and four major Mycobacterium tuberculosis complex lineages (L1, L3, L4, and L7) were identified with a predominance of the Euro-American L4 (72, 54.7%), while L7 genotypes were less common (3, 2.3%). Overall, the L4-T3-ETH (41, 32.0%), L3-CAS1-Delhi (29, 22.7%), and L3-CAS1-Killi (19, 14.8%) families were most common. Line probe analysis showed that among rpoB mutants, 65.2% were S450L, while 87.8% of katG mutants were S315T. Only three isolates showed mutation (c-15t) at the inhA gene, and no double mutation with katG and inhA genes was found. Six strains, two each of L1, L3, and L4, were resistant to FQs, having gyrA mutations (D94G, S91P), of which three isolates had additional resistance to SLI (rrs A1401G or C1402T mutations) including one isolate with low-level kanamycin (KAN) resistance.
CONCLUSIONS: This study showed a predominance of L4-T3-ETH, L3-CAS1-Delhi, and L3-CAS1-Killi families, with a high rate of rpoB_S450L and katG_S315T mutations and a low proportion of gyrA and rrs mutations. L7 was less frequently observed in this study. Further investigations are, therefore, needed to understand L7 and other lineages with undefined mutations.

DOI: 10.1016/j.jgar.2022.11.012
PMID: 36470362 [Indexed for MEDLINE]

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

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

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

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

BACKGROUND: Tuberculosis (TB) continues to be a common disease in developing countries, among which middle ear TB is rare. Furthermore, it is relatively difficult to make an early diagnosis and provide follow-up treatment for middle ear TB. So, it is necessary to report this case for reference and further discussion.
CASE PRESENTATION: We reported 1 case of multidrug-resistant tuberculosis otitis

media. TB otitis media is rare in tuberculosis; multidrug-resistant TB otitis media is even more rare. Our paper analyzes the possible causes, imaging, molecular biology, pathology, and clinical manifestations of multidrug-resistant TB otitis media.
CONCLUSION: PCR and DNA molecular biology techniques are highly recommended for the early diagnosis of multidrug-resistant TB otitis media. Early, effective anti-tuberculosis treatment is the guarantee for further recovery for patients with multidrug-resistant TB otitis media.

DOI: 10.1016/j.jctube.2023.100355
PMCID: PMC10011421
PMID: 36926472

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

11. **The differences in drug resistance between drug-resistant tuberculosis patients with and without diabetes mellitus in northeast China: a retrospective study.**

BMC Infect Dis. 2023 Mar 15;23(1):162. doi: 10.1186/s12879-023-08130-1.

Pan Y(1), Yu Y(1), Yi Y(1), Dou X(1), Lu J(1), Zhou L(2).

BACKGROUND: Diabetes mellitus (DM) and drug-resistant tuberculosis (DR-TB) are serious global public health problems. This study aimed to explore the differences in drug resistance between DR-TB patients with and without DM. Risk factors for developing multidrug-resistant tuberculosis (MDR-TB) were also investigated among DR-TB patients.
METHODS: The patient's basic demographic, clinical characteristics, and drug susceptibility testing (DST) data were collected from the Chinese Disease Control Information System. Descriptive statistics were used to estimate the frequency and proportion of included variables. Categorical variables were compared using the Chi-square test or Fisher's exact test. Chi-square tests for trends were used to determine changes and trends in MDR-TB and pre-extensively drug-resistantTB (pre-XDR-TB) patterns over time. Univariate and multivariate logistic regression analysis was used to explore the risk factors of MDR-TB.
RESULTS: Compared with DR-TB patients with DM, DR-TB patients without DM had significantly higher rates of mono-resistant streptomycin (SM) and any resistance to kanamycin (KM), but significantly lower rates of any resistance to protionamide (PTO) and mono-resistance to levofloxacin (LFX), and pre-XDR-TB

(P<0.05). The proportion of resistance to other anti-TB drugs was not statistically different between the DR-TB with and without DM. Among DR-TB patients without and with DM, the proportion of patients with MDR-TB and pre-XDR-TB patterns showed a significant downward trend from 2016 to 2021 (P<0.05). Among DR-TB patients without DM, male, previously treated DR-TB cases, and immigration were risk factors for MDR-TB (P<0.05). In DR-TB patients with DM, a negative sputum smear is a risk factor for MDR-TB (P<0.05). CONCLUSION: There was no statistical difference in resistance patterns between DR-TB with and without DM, except in arbitrary resistance to PTO and KM, mono-resistant SM and LFX, and pre-XDR-TB. Great progress has been made in the prevention and control of MDR-TB and pre-XDR-TB. However, DR-TB patients with and without DM differ in their risk factors for developing MDR-TB.

DOI: 10.1186/s12879-023-08130-1
PMCID: PMC10016172
PMID: 36922787 [Indexed for MEDLINE]

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

12. **Socioeconomic disparities and multidrug-resistant tuberculosis in South Korea: Focus on immigrants and income levels.**

J Microbiol Immunol Infect. 2023 Apr;56(2):424-428. doi: 10.1016/j.jmii.2022.08.014. Epub 2022 Sep 7.

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

Risk factors of MDR-TB remain unclear in South Korea, despite being an important public health issue. Findings from this study, which included ≥50,000 patients with TB from South Korea, suggests that immigrants and patients with lower income levels were strong predictors of MDR-TB in a high-income, high TB incidence country.

DOI: 10.1016/j.jmii.2022.08.014
PMID: 36115791 [Indexed for MEDLINE]

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

13. **Co-Delivery of D-LAK Antimicrobial Peptide and Capreomycin as Inhaled Powder Formulation to Combat Drug-Resistant Tuberculosis.**

Pharm Res. 2023 Mar 3:1-14. doi: 10.1007/s11095-023-03488-y. Online ahead of print.

Shao Z(1), Chow MYT(1)(2), Chow SF(1)(3), Lam JKW(4)(5)(6).

INTRODUCTION: The emergence of multidrug-resistant (MDR) Mycobacterium tuberculosis (Mtb) posed a severe challenge to tuberculosis (TB) management. The treatment of MDR-TB involves second-line anti-TB agents, most of which are injectable and highly toxic. Previous metabolomics study of the Mtb membrane revealed that two antimicrobial peptides, D-LAK120-A and D-LAK120-HP13, can potentiate the efficacy of capreomycin against mycobacteria.
AIMS: As both capreomycin and peptides are not orally available, this study aimed to formulate combined formulations of capreomycin and D-LAK peptides as inhalable dry powder by spray drying.
METHODS AND RESULTS: A total of 16 formulations were prepared with different levels of drug content and capreomycin to peptide ratios. A good production yield of over 60% (w/w) was achieved in most formulations. The co-spray dried particles exhibited spherical shape with a smooth surface and contained low residual moisture of below 2%. Both capreomycin and D-LAK peptides were enriched at the surface of the particles. The aerosol performance of the formulations was evaluated with Next Generation Impactor (NGI) coupled with Breezhaler®. While no significant difference was observed in terms of emitted fraction (EF) and fine particle fraction (FPF) among the different formulations, lowering the flow rate from 90 L/min to 60 L/min could reduce the impaction at the throat and improve the FPF to over 50%.
CONCLUSIONS: Overall, this study showed the feasibility of producing co-spray dried formulation of capreomycin and antimicrobial peptides for pulmonary delivery. Future study on their antibacterial effect is warranted.

DOI: 10.1007/s11095-023-03488-y
PMCID: PMC9984245
PMID: 36869245

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

15. **Pharmacokinetics of Antituberculosis Drugs in Plasma and Cerebrospinal Fluid in**

a Patient with Pre-Extensive Drug Resistant Tuberculosis Meningitis.

Infect Drug Resist. 2023 Mar 23;16:1669-1676. doi: 10.2147/IDR.S401281. eCollection 2023.

Liang Z(#)(1), Liao W(#)(2), Chen Q(3), Li H(1), Ye M(1), Zou J(4), Deng G(1), Zhang P(1).

Drug-resistant tuberculous meningitis (TBM) is the most devastating and critical form of extrapulmonary tuberculosis. Here, we present a case of a 45-year-old male with pre-extensive drug-resistant tuberculosis meningitis (pre-XDR-TBM). He underwent emergency surgery for the long-tunneled external ventricular drainage (LTEVD). Molecular test and phenotypic drug sensitivity test (DST) of Mycobacterium tuberculosis in cerebrospinal fluid (CSF) showed that the isolate was resistant to both rifampin and fluoroquinolones. An anti-tuberculous regimen of isoniazid, pyrazinamide, cycloserine, moxifloxacin, clofazimine, and linezolid was tailored accordingly. We monitored the drug concentration in his plasma and CSF before (at 0-hour) and after anti-TB drugs administration (at 1-hour, 2-hour, 6-hour, and 12-hour) on 10th day after treatment initiation. We hope to provide reference values of drug exposures in plasma and CSF for patients with pre-XDR-TBM.

DOI: 10.2147/IDR.S401281
PMCID: PMC10041991
PMID: 36992966

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

16. **Tuberculosis in the Russian Federation: Prognosis and Epidemiological Models in a Situation After the COVID-19 Pandemic.**

J Epidemiol Glob Health. 2023 Mar;13(1):11-22. doi: 10.1007/s44197-023-00085-5. Epub 2023 Feb 6.

Starshinova A(1), Belyaeva E(2), Doktorova N(3), Korotkevich I(3), Kudlay D(4)(5).

AIM: Because of the COVID-19 pandemic, many support programs for tuberculosis (TB) patients have been discontinued and TB mass screening activities decreased worldwide, resulting in a decrease in new case detection and an increase in TB

deaths (WHO, WHO global lists of high burden countries for TB, multidrug/rifampicin-resistant TB (MDR/RR-TB) and TB/HIV, 2021-2025, 2021). The study aimed to assess changes in epidemiological indicators of tuberculosis in the Russian Federation and to simulate these indicators in the post-COVID-19 period.
MATERIALS AND METHODS: The main epidemiological indicators of tuberculosis were analyzed with the use of government statistical data for the period from 2009 to 2021. Further mathematical modeling of epidemiological indicators for the coming years was carried out, taking into account the TB screening by chest X-ray. Statistical analysis was carried out using the software environment R (v.3.5.1) for statistical computing and the commercial software Statistical Package for the Social Sciences (SPSS Statistics for Windows, version 24.0, IBM Corp., 2016). Time series forecasting was performed using the programming language for statistical calculations R, version 4.1.2 and the bsts package, version 0.9.8.
STUDY RESULTS: The study has found that the mean regression coefficient of a single predictor differs in the model for TB incidence and mortality (0.0098 and 0.0002, respectively). Forecast of overall incidence, the incidence of children and the forecast for mortality using the basic scenario (screening 75-78%) for the period from 2022 to 2026 was characterized by a mean decrease rate of 23.1%, 15.6% and 6.0% per year, respectively. A conservative scenario (screening 47-63%) of overall incidence indicates that the incidence of children and the forecast for mortality will continue to decrease with a mean decrease rate of 23.2%, 15.6% and 6.0% per year, respectively. Comparable data were obtained from the forecast of overall incidence, the incidence of children and the forecast for mortality using the optimistic scenario (screening 82-89%) with a mean decrease rate of 22.9%, 15.4% and 6.0% per year, respectively.
CONCLUSIONS: It has been proven that the significance of screening with chest X-ray as a predictor of mortality is minimal. However, TB screening at least 60% of the population (chest X-ray in adults and immunological tests in children) have provided relationship between the TB screening rate and TB mortality rate (TB mortality rate increases with an increase in the population coverage and, conversely, decreases with a decrease in the population coverage).

DOI: 10.1007/s44197-023-00085-5
PMCID: PMC9900203
PMID: 36740623 [Indexed for MEDLINE]

Conflict of interest statement: None to declare.

17. **Drug-Resistant Tuberculosis on the Balkan Peninsula: Determination of Drug Resistance Mechanisms with Xpert MTB/XDR and Whole-Genome Sequencing Analysis.**

Microbiol Spectr. 2023 Mar 6:e0276122. doi: 10.1128/spectrum.02761-22. Online ahead of print.

Truden S(1), Sodja E(1), Žolnir-Dovč M(1).

The new molecular assay Xpert MTB/XDR (Cepheid, Sunnyvale, CA, USA) was launched in 2021 to detect Mycobacterium tuberculosis (MT) complex with mutations conferring resistance to isoniazid (INH), ethionamide (ETH), fluoroquinolone (FQ), and second-line injectable drugs (SLIDs). The aim of our study was to evaluate the performance of the Xpert MTB/XDR rapid molecular assay on rifampicin-resistant, multidrug-resistant, and pre-extensively resistant tuberculosis (TB) isolates in a clinical laboratory in the Balkan Peninsula compared to a phenotypic drug susceptibility test (pDST). Xpert MTB/XDR was used to test positive Bactec MGIT 960 (Becton, Dickinson and Co., Franklin Lakes, NJ, USA) cultures or DNA isolates. In the case of discrepant results between Xpert MTB/XDR and pDST, the usefulness of whole-genome sequencing (WGS) was emphasized. In our study, 80 MT isolates from different Balkan countries were selectively chosen from the National Mycobacterial Strain Collection in Golnik, Slovenia. Isolates were tested with the Xpert MTB/XDR assay, conventional pDST, and WGS. Xpert MTB/XDR showed high sensitivities of 91.9%, 100%, and 100% for detecting INH, FQ, and SLID resistance, respectively, compared to pDST. In contrast, low sensitivity (51.9%) for ETH resistance was achieved because isolates harbored widespread mutations across the ethA gene. The specificity of Xpert MTB/XDR was 100% for all drugs except for INH (66.7%). Further investigation with WGS revealed -57c→t mutations in the oxyR-ahpC region marked with uncertain significance, which caused the low specificity for detecting INH resistance with the new assay. Xpert MTB/XDR can be used in clinical laboratories for the rapid detection of INH, FQ, and SLID resistance. Moreover, it can be used to rule in resistance to ETH. Additional use of WGS is recommended in cases of discrepant results between pDST and Xpert MTB/XDR. Future improvements of Xpert MTB/XDR with the inclusion of additional genes may increase the usefulness of the assay. IMPORTANCE The Xpert MTB/XDR was tested on drug-resistant Mycobacterium tuberculosis complex isolates from the Balkan Peninsula. Positive Bactec MGIT 960 cultures or DNA isolates were tested as starting material. According to the results of our study with Xpert MTB/XDR, sensitivities for the detection of SLID, FQ, and INH resistance were sufficient (>90%) for the assay to be implemented into diagnostic algorithms. In our study, WGS revealed lesser-known mutations in genes conferring INH and ETH resistance, and their impact on resistance is still unknown. Mutations in the ethA gene causing resistance to ETH were scattered along structural gene without high-confidence markers for resistance. Therefore, resistance to ETH should be reported based on a combination of methods. Because the Xpert MTB/XDR assay was found to have good performance, we propose that it should be the method of

choice for confirming resistance to INH, FQ, and SLID and conditionally for resistance to ETH.

DOI: 10.1128/spectrum.02761-22
PMID: 36877052

18. **Genomic Sequencing from Sputum for Tuberculosis Disease Diagnosis, Lineage Determination, and Drug Susceptibility Prediction.**

J Clin Microbiol. 2023 Mar 23;61(3):e0157822. doi: 10.1128/jcm.01578-22. Epub 2023 Feb 23.

Nilgiriwala K(#)(1), Rabodoarivelo MS(#)(2), Hall MB(#)(3)(4), Patel G(1), Mandal A(1), Mishra S(1), Andrianomanana FR(2), Dingle K(5), Rodger G(5), George S(5), Crook DW(5), Hoosdally S(5), Mistry N(1), Rakotosamimanana N(2), Iqbal Z(3), Grandjean Lapierre S(#)(2)(6)(7), Walker TM(#)(5)(8).

Universal access to drug susceptibility testing for newly diagnosed tuberculosis patients is recommended. Access to culture-based diagnostics remains limited, and targeted molecular assays are vulnerable to emerging resistance mutations. Improved protocols for direct-from-sputum Mycobacterium tuberculosis sequencing would accelerate access to comprehensive drug susceptibility testing and molecular typing. We assessed a thermo-protection buffer-based direct-from-sample M. tuberculosis whole-genome sequencing protocol. We prospectively analyzed 60 acid-fast bacilli smear-positive clinical sputum samples in India and Madagascar. A diversity of semiquantitative smear positivity-level samples were included. Sequencing was performed using Illumina and MinION (monoplex and multiplex) technologies. We measured the impact of bacterial inoculum and sequencing platforms on genomic read depth, drug susceptibility prediction performance, and typing accuracy. M. tuberculosis was identified by direct sputum sequencing in 45/51 samples using Illumina, 34/38 were identified using MinION-monoplex sequencing, and 20/24 were identified using MinION-multiplex sequencing. The fraction of M. tuberculosis reads from MinION sequencing was lower than from Illumina, but monoplexing grade 3+ samples on MinION produced higher read depth than Illumina ($P < 0.05$) and MinION multiplexing ($P < 0.01$). No significant differences in sensitivity and specificity of drug susceptibility predictions were seen across sequencing modalities or within each technology when stratified by smear grade. Illumina sequencing from sputum accurately identified 1/8 (rifampin) and 6/12 (isoniazid) resistant samples, compared to 2/3 (rifampin) and 3/6 (isoniazid) accurately identified with Nanopore monoplex. Lineage agreement levels between direct and culture-based sequencing were 85% (MinION-monoplex), 88% (Illumina), and 100%

(MinION-multiplex). M. tuberculosis direct-from-sample whole-genome sequencing remains challenging. Improved and affordable sample treatment protocols are needed prior to clinical deployment.

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PMCID: PMC10035339
PMID: 36815861 [Indexed for MEDLINE]

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

19. **Medicinal Plants as Therapeutic Alternatives to Combat Mycobacterium tuberculosis: A Comprehensive Review.**

Antibiotics (Basel). 2023 Mar 8;12(3):541. doi: 10.3390/antibiotics12030541.

Gautam S(1), Qureshi KA(2), Jameel Pasha SB(1), Dhanasekaran S(3), Aspatwar A(4), Parkkila S(4)(5), Alanazi S(6), Atiya A(7), Khan MMU(8), Venugopal D(1).

Tuberculosis (TB) is a serious infectious disease caused by Mycobacterium tuberculosis (MTB) and a significant health concern worldwide. The main threat to the elimination of TB is the development of resistance by MTB to the currently used antibiotics and more extended treatment methods, which is a massive burden on the health care system. As a result, there is an urgent need to identify new, effective therapeutic strategies with fewer adverse effects. The traditional medicines found in South Asia and Africa have a reservoir of medicinal plants and plant-based compounds that are considered another reliable option for human beings to treat various diseases. Abundant research is available for the biotherapeutic potential of naturally occurring compounds in various diseases but has been lagging in the area of TB. Plant-based compounds, or phytoproducts, are being investigated as potential anti-mycobacterial agents by reducing bacterial burden or modulating the immune system, thereby minimizing adverse effects. The efficacy of these phytochemicals has been evaluated through drug delivery using nanoformulations. This review aims to emphasize the value of anti-TB compounds derived from plants and provide a summary of current research on phytochemicals with potential anti-mycobacterial activity against MTB. This article aims to inform readers about the numerous potential herbal treatment options available for combatting TB.

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PMID: 36978408

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

20. **Perchlozone Resistance in Clinical Isolates of Mycobacterium tuberculosis.**

Antibiotics (Basel). 2023 Mar 15;12(3):590. doi: 10.3390/antibiotics12030590.

Ushtanit A(1), Mikhailova Y(2), Krylova L(2), Grigorash D(3), Makarova M(2), Safonova S(2), Zimenkov D(1).

The emergence of drug-resistant tuberculosis forced the development of new drugs and the screening of more effective or less toxic analogues. Mycolic acid biosynthesis is targeted by several antituberculosis drugs, isoniazid being one of the most important in tuberculosis therapy. Recently, perchlozone, acting on another step in the FAS-II cycle, was officially approved for tuberculosis treatment in the Russian Federation and was included in the Russian national clinical guidelines. Using the serial dilution method on 7H10 agar plates for perchlozone and a Sensititre MYCOTB microdilution plate, we analyzed the phenotypic properties of primary clinical isolates of M. tuberculosis and analyzed the molecular determinants of resistance to isoniazid, ethionamide, and perchlozone. We found a wide variation in the MIC of perchlozone from 2 to 64 mg/L, correlating with the overall resistance profile: the MIC was higher for MDR and pre-XDR isolates. The cross-resistance between ethionamide and perchlozone was driven by mutations in the ethA gene encoding monooxygenase responsible for the activation of both drugs. The presumably susceptible to perchlozone and wild-type strains had MICs ranging from 2 to 4 mg/L, and the breakpoint was estimated to be 4 or 8 mg/L. In conclusion, susceptibility to perchlozone is retained for a part of the MDR strains, as is susceptibility to ethionamide, providing the possibility of therapy for such cases based on phenotypic or molecular analysis.

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PMCID: PMC10044601
PMID: 36978456

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21. **Prevalence of long-term physical sequelae among patients treated with multi-drug and extensively drug-resistant tuberculosis: a systematic review and**

meta-analysis.

EClinicalMedicine. 2023 Mar 10;57:101900. doi: 10.1016/j.eclinm.2023.101900. eCollection 2023 Mar.

Akalu TY(1)(2)(3), Clements ACA(1)(2)(4), Wolde HF(1)(2)(3), Alene KA(1)(2)(3).

BACKGROUND: Physical sequelae related to multi-drug resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) are emerging and under-recognised global challenges. This systematic review and meta-analysis aimed to quantify the prevalence and the types of long-term physical sequelae associated with patients treated for MDR- and XDR-TB.
METHODS: We systematically searched CINAHL (EBSCO), MEDLINE (via Ovid), Embase, Scopus, and Web of Science from inception through to July 1, 2022, and the last search was updated to January 23, 2023. We included studies reporting physical sequelae associated with all forms of drug-resistant TB, including rifampicin-resistant TB (RR-TB), MDR-TB, Pre-XDR-TB, and XDR-TB. The primary outcome of interest was long-term physical sequelae. Meta-analysis was conducted using a random-effect model to estimate the pooled proportion of physical sequelae. The sources of heterogeneity were explored through meta-regression using study characteristics as covariates. The research protocol was registered in PROSPERO (CRD42021250909).
FINDINGS: From 3047 unique publications identified, 66 studies consisting of 37,380 patients conducted in 30 different countries were included in the meta-analysis. The overall pooled estimate was 44.4% (95% Confidence Interval (CI): 36.7-52.1) for respiratory sequelae, 26.7% (95% CI: 23.85-29.7) for hearing sequelae, 10.1% (95% CI: 7.0-13.2) for musculoskeletal sequelae, 8.4% (95% CI: 6.5-10.3) for neurological sequelae, 8.1% (95% CI: 6.3-10.0) for renal sequelae, 7.3% (95% CI: 5.1-9.4) for hepatic sequelae, and 4.5% (95% CI: 2.7-6.3) for visual sequelae. There was substantial heterogeneity in the estimates. The stratified analysis showed that the pooled prevalence of hearing sequelae was 26.6% (95% CI: 12.3-40.9), neurological sequelae was 31.5% (95% CI: 5.5-57.5), and musculoskeletal sequelae were 21.5% (95% CI: 9.9-33.1) for patients with XDR-TB, which were higher than the pooled prevalence of sequelae among patients with MDR-TB. Respiratory sequelae were the highest in low-income countries (59.3%) and after completion of MDR-TB treatment (57.7%).
INTERPRETATION: This systematic review found that long-term physical sequelae such as respiratory, hearing, musculoskeletal, neurological, renal, hepatic, and visual sequelae were common among survivors of MDR- and XDR-TB. There was a significant difference in the prevalence of sequelae between patients with MDR- and XDR-TB. Post-MDR- and XDR-TB treatment surveillance for adverse outcomes needs to be incorporated into the current programmatic management of MDR-TB to enable early detection and prevention of post-treatment sequelae.
FUNDING: Australian National Health and Medical Research Council, through an

Emerging Leadership Investigator grant, and the Curtin University Higher Degree Research scholarship.

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PMID: 36942158

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

22. **Prevalence and factors associated with reported adverse-events among patients on multi-drug-resistant tuberculosis treatment in two referral hospitals in Uganda.**

BMC Infect Dis. 2023 Mar 10;23(1):149. doi: 10.1186/s12879-023-08085-3.

Ategyeka PM(1), Muhoozi M(2)(3), Naturinda R(2), Kageni P(4), Namugenyi C(5), Kasolo A(6), Kisaka S(2)(7)(8), Kiwanuka N(2).

BACKGROUND: Multi-drug-resistant tuberculosis (MDR-TB) treatment involves toxic drugs that cause adverse events (AEs), which are life-threatening and may lead to death if not well managed. In Uganda, the prevalence of MDR-TB is increasingly high, and about 95% of the patients are on treatment. However, little is known about the prevalence of AEs among patients on MDR-TB medicines. We therefore estimated the prevalence of reported adverse events (AEs) of MDR-TB drugs and factors associated with AEs in two health facilities in Uganda.
METHODS: A retrospective cohort study of MDR-TB was conducted among patients enrolled at Mulago National Referral and Mbarara Regional Referral hospitals in Uganda. Medical records of MDR-TB patients enrolled between January 2015 and December 2020 were reviewed. Data on AEs, which were defined as irritative reactions to MDR-TB drugs, were extracted and analyzed. To describe reported AEs, descriptive statistics were computed. A modified Poisson regression analysis was used to determine factors associated with reported AEs.
RESULTS: Overall, 369 (43.1%) of 856 patients had AEs, and 145 (17%) of 856 had more than one. Joint pain (244/369, or 66%), hearing loss (75/369, or 20%), and vomiting (58/369, or 16%) were the most frequently reported effects. Patients started on the 24-month regimen (adj. PR = 1.4, 95%; 1.07, 1.76) and individualized regimens (adj. PR = 1.5, 95%; 1.11, 1.93) were more likely to suffer from AEs. Lack of transport for clinical monitoring (adj. PR = 1.9, 95%; 1.21, 3.11); alcohol consumption (adj. PR = 1.2, 95%; 1.05, 1.43); and receipt of directly observed therapy from peripheral health facilities (adj. PR = 1.6, 95%; 1.10, 2.41) were significantly associated with experiencing AEs. However,

patients who received food supplies (adj. PR = 0.61, 95%; 0.51, 0.71) were less likely to suffer from AEs.
CONCLUSION: The frequency of adverse events reported by MDR-TB patients is considerably high, with joint pain being the most common. Interventions such as the provision of food supplies, transportation, and consistent counseling on alcohol consumption to patients at initiation treatment facilities may contribute to a reduction in the rate of occurrence of AEs.

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PMID: 36899299 [Indexed for MEDLINE]

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

23. **Impact of COVID-19 on diagnosis of TB, MDR-TB and on mortality in 11 countries in Europe, Northern America and Australia. A Global Tuberculosis Network study.**

Int J Infect Dis. 2023 Mar 7:S1201-9712(23)00076-0. doi: 10.1016/j.ijid.2023.02.025. Online ahead of print.

Nalunjogi J(1), Mucching-Toscano S(2), Sibomana JP(3), Centis R(4), D'Ambrosio L(5), Alffenaar JW(6), Denholm J(7), Blanc FX(8), Borisov S(9), Danila E(10), Duarte R(11), García-García JM(12), Goletti D(13), Ong CWM(14), Rendon A(15), Thomas TA(16), Tiberi S(17), van den Boom M(18), Sotgiu G(19), Migliori GB(20); Global Tuberculosis Network.

OBJECTIVE: Although evidence is growing on the overall impact of the COVID-19 pandemic on tuberculosis (TB) services, global studies based on national data are needed to better quantify the extent of the impact and the countries' preparedness to tackle the two diseases. The aim of this study was to compare the number of people with new diagnosis or recurrence of TB disease, the number of drug-resistant (DR)-TB, and the number of TB deaths in 2020 versus 2019 in 11 countries in Europe, Northern America and Australia.
METHODS: TB managers or directors of national reference centres of the selected countries provided the agreed-upon variables through a validated questionnaire on a monthly basis. A descriptive analysis compared incidence of TB and drug-resistant TB and mortality of the pre-COVID-19 year (2019) versus the first year of the COVID-19 pandemic (2020).
RESULTS: Comparing 2020 vs 2019, lower number of TB cases (new diagnosis or recurrence) was notified in all countries (except USA-Virginia and Australia),

and less DR-TB notifications (apart from France, Portugal and Spain). The deaths among TB cases were higher in 2020 compared to 2019 in most countries with three countries (France, Netherlands, USA-Virginia) reporting minimal TB-related mortality.

DOI: 10.1016/j.ijid.2023.02.025
PMCID: PMC9991328
PMID: 36893943

24. **In vitro and in silico evaluations of actinomycin X(2)and actinomycin D as potent anti-tuberculosis agents.**

PeerJ. 2023 Mar 8;11:e14502. doi: 10.7717/peerj.14502. eCollection 2023.

Qureshi KA(1), Azam F(2), Fatmi MQ(3), Imtiaz M(3), Prajapati DK(4), Rai PK(4), Jaremko M(5), Emwas AH(6), Elhassan GO(1).

BACKGROUND: Multidrug-resistant tuberculosis (MDR-TB) is one of the world's most devastating contagious diseases and is caused by the MDR-Mycobacterium tuberculosis (MDR-Mtb) bacteria. It is therefore essential to identify novel anti-TB drug candidates and target proteins to treat MDR-TB. Here, in vitro and in silico studies were used to investigate the anti-TB potential of two newly sourced actinomycins, actinomycin-X2 (act-X2) and actinomycin-D (act-D), from the Streptomyces smyrnaeus strain UKAQ_23 (isolated from the Jubail industrial city of Saudi Arabia).
METHODS: The anti-TB activity of the isolated actinomycins was assessed in vitro using the Mtb H37Ra, Mycobacterium bovis (BCG), and Mtb H37Rv bacterial strains, using the Microplate Alamar Blue Assay (MABA) method. In silico molecular docking studies were conducted using sixteen anti-TB drug target proteins using the AutoDock Vina 1.1.2 tool. The molecular dynamics (MD) simulations for both actinomycins were then performed with the most suitable target proteins, using the GROningen MAchine For Chemical Simulations (GROMACS) simulation software (GROMACS 2020.4), with the Chemistry at HARvard Macromolecular Mechanics 36m (CHARMM36m) forcefield for proteins and the CHARMM General Force Field (CGenFF) for ligands.
RESULTS: In vitro results for the Mtb H37Ra, BCG, and Mtb H37Rv strains showed that act-X2 had minimum inhibitory concentration (MIC) values of 1.56 ± 0.0, 1.56 ± 0.0, and 2.64 ± 0.07 µg/mL and act-D had MIC values of 1.56 ± 0.0, 1.56 ± 0.0, and 1.80 ± 0.24 µg/mL respectively. The in silico molecular docking results showed that protein kinase PknB was the preferred target for both actinomycins, while KasA and pantothenate synthetase were the least preferred

targets for act-X2and act-D respectively. The molecular dynamics (MD) results demonstrated that act-X2 and act-D remained stable inside the binding region of PknB throughout the simulation period. The MM/GBSA (Molecular Mechanics/Generalized Born Surface Area) binding energy calculations showed that act-X2 was more potent than act-D.
CONCLUSION: In conclusion, our results suggest that both actinomycins X2 and D are highly potent anti-TB drug candidates. We show that act-X2is better able to antagonistically interact with the protein kinase PknB target than act-D, and thus has more potential as a new anti-TB drug candidate.

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PMCID: PMC10022501
PMID: 36935926 [Indexed for MEDLINE]

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

25. **Retaining Patients with Drug-Resistant Tuberculosis on Treatment During the COVID-19 Pandemic - Dharavi, Mumbai, India, 2020-2022.**

MMWR Morb Mortal Wkly Rep. 2023 Mar 24;72(12):304-308. doi: 10.15585/mmwr.mm7212a2.

Gomare MD, Bhide S, Deshmukh R, Kaipilyawar S, Puri V, Moonan PK, Khetade DK, Nyendak M, Yeldandi V, Smith JP, Tobias JL, Date A, Joshi R, Kumar R, Ho CS.

Mumbai, India's second largest city, has one of the highest prevalences of drug-resistant tuberculosis* (DRTB) in the world. Treatment for DRTB takes longer and is more complicated than treatment for drug-susceptible tuberculosis (TB). Approximately 300 persons receive a new DRTB diagnosis each year in Mumbai's Dharavi slum†; historically, fewer than one half of these patients complete DRTB treatment. As nationwide restrictions to mitigate the COVID-19 pandemic were implemented, a program to facilitate uninterrupted DRTB care for patients receiving treatment was also implemented. A comprehensive tool and risk assessment provided support to DRTB patients and linked those who relocated outside of Dharavi during the pandemic to DRTB care at their destination. During May 2020-September 2022, a total of 973 persons received DRTB treatment in Dharavi, including 255 (26%) who relocated during treatment. Overall, 25 (3%) DRTB patients were lost to follow-up, a rate substantially lower than the rate before the pandemic (18%). Proactive planning and implementation of simple tools retained patients on treatment during periods of travel restrictions and

relocations, improving programmatic outcomes. This approach might aid public health programs serving migrant populations or patients receiving treatment for DRTB during public health emergencies.

DOI: 10.15585/mmwr.mm7212a2
PMCID: PMC10042620
PMID: 36952291 [Indexed for MEDLINE]

Conflict of interest statement: All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. No potential conflicts of interest were disclosed.

26. **Discovery of natural-product-derived sequanamycins as potent oral anti-tuberculosis agents.**

Cell. 2023 Mar 2;186(5):1013-1025.e24. doi: 10.1016/j.cell.2023.01.043. Epub 2023 Feb 23.

Zhang J(1), Lair C(2), Roubert C(2), Amaning K(1), Barrio MB(3), Benedetti Y(1), Cui Z(4), Xing Z(4), Li X(4), Franzblau SG(5), Baurin N(1), Bordon-Pallier F(1), Cantalloube C(6), Sans S(2), Silve S(2), Blanc I(2), Fraisse L(2), Rak A(1), Jenner LB(7), Yusupova G(7), Yusupov M(7), Zhang J(4), Kaneko T(8), Yang TJ(8), Fotouhi N(8), Nuermberger E(9), Tyagi S(9), Betoudji F(9), Upton A(10), Sacchettini JC(11), Lagrange S(2).

The emergence of drug-resistant tuberculosis has created an urgent need for new anti-tubercular agents. Here, we report the discovery of a series of macrolides called sequanamycins with outstanding in vitro and in vivo activity against Mycobacterium tuberculosis (Mtb). Sequanamycins are bacterial ribosome inhibitors that interact with the ribosome in a similar manner to classic macrolides like erythromycin and clarithromycin, but with binding characteristics that allow them to overcome the inherent macrolide resistance of Mtb. Structures of the ribosome with bound inhibitors were used to optimize sequanamycin to produce the advanced lead compound SEQ-9. SEQ-9 was efficacious in mouse models of acute and chronic TB as a single agent, and it demonstrated bactericidal activity in a murine TB infection model in combination with other TB drugs. These results support further investigation of this series as TB clinical candidates, with the potential for use in new regimens against drug-susceptible and drug-resistant TB.

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PMCID: PMC9994261
PMID: 36827973 [Indexed for MEDLINE]

Conflict of interest statement: Declaration of interests Jidong Zhang, K.A., Y.B., N.B., F.B.-P., C.C., and A.R. are employed by Sanofi R&D. C.L., C.R., S. Sans, S. Silve, I.B., and S.L. were employed by Sanofi R&D and now Evotec. M.B.B. was employed by Sanofi R&D and now Inrae, France. L.F. was employed by Sanofi R&D and now Drugs for Neglected Diseases initiative (DNDi), Switzerland.

27. **Time to commencement of effective treatment in patients with drug-resistant tuberculosis diagnosed in the Torres Strait-Papua New Guinea cross-border region.**

Rural Remote Health. 2023 Mar;23(1):7165. doi: 10.22605/RRH7165. Epub 2023 Mar 28.

Foster J(1), Mendez D(2), Marais B(3), Peniyamina D(4), McBryde E(5).

INTRODUCTION: Delays between self-reported symptom onset and commencement of effective treatment contribute to ongoing tuberculosis (TB) transmission, which is a particular concern in patients with drug-resistant (DR)-TB. The study authors assessed improvements in time to commencement of effective treatment in patients diagnosed with DR-TB in the Torres Strait-Papua New Guinea cross-border region.
METHODS: All laboratory-confirmed DR-TB cases diagnosed in the Torres Strait between 1 March 2000 and 31 March 2020 were reviewed. Total time from self-reported onset of symptoms to effective treatment commencement in different programmatic time periods was assessed. Pairwise analyses and time to event proportional hazard calculations were used to explore the association between delays in median time to effective treatment, and selected variables. Data were further analysed to examine predictors of excessive treatment delay.
RESULTS: The median number of days from self-reported onset of symptoms to effective treatment commencement was 124 days (interquartile range 51-214) over two decades. Between 2006 and 2012, most (57%) cases exceeded this 'grand median' while the median 'time to treat' in the most recent time period (2016-2020) was significantly reduced to 29 days ($p<0.001$). Although there was a reduction in the median 'time to treat' with the introduction of Xpert MTB/RIF (135 days pre-Xpert v 67 days post-Xpert) this was not statistically significant ($p=0.07$). Establishment of the Torres and Cape TB Control Unit on Thursday Island (2016-2020) was significantly associated with reduced treatment delay, compared to the previous TB program period (2000-2005, $p<0.04$; 2006-2012, $p<0.001$).

CONCLUSION: Minimising TB treatment delay in remote settings like the Torres Strait-Papua New Guinea cross-border region requires effective decentralised diagnosis and management structures. The results of this study suggest that the establishment of the Torres and Cape TB Control Unit on Thursday Island significantly improved time to commencement of effective TB treatment. Possible contributing factors include better TB education, cross-border communication and patient-centred care.

DOI: 10.22605/RRH7165
PMID: 36977420 [Indexed for MEDLINE]

28. **The socio-demographic, clinical characteristics and outcomes of tuberculosis among HIV infected adults in Lithuania: A thirteen-year analysis.**

PLoS One. 2023 Mar 23;18(3):e0282046. doi: 10.1371/journal.pone.0282046. eCollection 2023.

Matulyte E(1)(2), Davidaviciene E(3), Kancauskiene Z(4), Diktanas S(5), Kausas A(6), Velyvyte D(7)(8), Urboniene J(2), Lipnickiene V(9), Laurencikaite M(10), Danila E(11)(12), Costagliola D(13), Matulionyte R(1)(2).

BACKGROUND: Tuberculosis (TB) is a public health problem in Lithuania, among the 18 high-priority TB countries in the European region, and the most common AIDS-indicative disease with the highest proportion in the EU/EEA since 2015. The study aimed to identify socio-demographic, clinical characteristics and their relationship with TB outcomes in TB-HIV co-infected patients in Lithuania.
METHODS: A retrospective chart review analysed the characteristics of TB-HIV co-infected adults registered in State Information System of Tuberculosis over 2008-2020. The factors associated with drug-resistant TB and unsuccessful treatment outcome were identified by multivariable logistic regression.
RESULTS: The study included 345 cases in 311 patients (239 new, 106 previously treated cases), median age 40 years (IQR 35-45), 80.7% male. 67.8% patients knew their HIV-positive status before TB diagnosis, median time to TB diagnosis was 8 years (IQR 4-12). 83.6% were unemployed, 50.5%-anytime intravenous drug users (IDU), 34.9% abused alcohol. Drug-resistant TB rates in new and previously treated TB cases were 38.1% and 61.3%, respectively. In multivariable analysis, higher risk of drug-resistant TB was associated with imprisonment in new (aOR 3.35; 95%CI 1.17-9.57) and previously treated (aOR 6.63; 95%CI 1.09-40.35) cases. In 52.3% of new TB cases and in 42.5% previously treated TB cases the treatment outcomes were unsuccessful. In multivariable analysis of new TB cases, current imprisonment (aOR 2.77; 95%CI 1.29-5.91) and drug-resistant TB (aOR 2.18; 95%CI 1.11-4.28) were associated with unsuccessful treatment outcome. In multivariable analysis of previously treated TB cases, female gender (aOR 11.93;

95%CI 1.86-76.69), alcohol abuse (aOR 3.17; 95%CI 1.05-9.58), drug-resistant TB (aOR 4.83; 95%CI 1.53-15.28) were associated with unsuccessful treatment outcome.
CONCLUSIONS: In the TB-HIV-infected adult cohort in Lithuania, unemployment, imprisonment, IDU, alcohol abuse, known to be risk factors for TB, were very frequent. Drug resistance was an undeniable risk factor for unsuccessful treatment outcome and imprisonment was associated with drug resistant TB.

DOI: 10.1371/journal.pone.0282046
PMCID: PMC10035857
PMID: 36952578 [Indexed for MEDLINE]

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

29. **Spatial Distribution of Drug-Resistant Mycobacterium tuberculosis Infections in Rural Eastern Cape Province of South Africa.**

Pathogens. 2023 Mar 17;12(3):475. doi: 10.3390/pathogens12030475.

Faye LM(1), Hosu MC(1), Vasaikar S(1), Dippenaar A(2), Oostvogels S(2), Warren RM(3), Apalata T(1).

Tuberculosis (TB), an infectious airborne disease caused by Mycobacterium tuberculosis (Mtb), is a serious public health threat reported as the leading cause of morbidity and mortality worldwide. South Africa is a high-TB-burden country with TB being the highest infectious disease killer. This study investigated the distribution of Mtb mutations and spoligotypes in rural Eastern Cape Province. The Mtb isolates included were 1157 from DR-TB patients and analysed by LPA followed by spoligotyping of 441 isolates. The distribution of mutations and spoligotypes was done by spatial analysis. The rpoB gene had the highest number of mutations. The distribution of rpoB and katG mutations was more prevalent in four healthcare facilities, inhA mutations were more prevalent in three healthcare facilities, and heteroresistant isolates were more prevalent in five healthcare facilities. The Mtb was genetically diverse with Beijing more prevalent and largely distributed. Spatial analysis and mapping of gene mutations and spoligotypes revealed a better picture of distribution.

DOI: 10.3390/pathogens12030475
PMCID: PMC10059723
PMID: 36986397

Conflict of interest statement: The authors declare no conflict of interest. The funders had no role in the design of this study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

30. **Potential and weak links in the management of tuberculosis by Pakistani private pharmacy staff.**

Front Public Health. 2023 Mar 9;11:983997. doi: 10.3389/fpubh.2023.983997. eCollection 2023.

Balquis F(1)(2), Sohail MF(1)(3), Hamid H(4), Ullah W(1)(2), Khan AH(5), Shahnaz G(1).

INTRODUCTION: The emergence of MDR-TB is a global threat and an obstacle to the effective control of TB in Pakistan. A lack of proper TB knowledge among the staff in private pharmacies and the sale of compromised quality anti-TB drugs are the main instigators of multidrug-resistant tuberculosis (MDR-TB). Thus, this study was aimed at investigating the quality and storage conditions of fixed-dose combination (FDC) anti-TB drugs along with the awareness of staff working in private pharmacies regarding the identification of potential patients with TB and dispensing the inappropriate treatment regimens contributing to MDR-TB.
METHODS: The study is completed in two phases. In phase I a cross-sectional study is performed using two quantitative research designs, i.e., exploratory and descriptive, to evaluate the knowledge of private pharmacy staff. The sample of 218 pharmacies was selected. While in phase II cross sectional survey is conducted in 10 facilities from where FDC anti TB drugs were sampled for analyzing their quality.
RESULT: Results revealed the presence of pharmacists only at 11.5% of pharmacies. Approximately 81% of staff at pharmacies had no awareness of MDR-TB, while 89% of pharmacies had no TB-related informative materials. The staff identified that most of the patients with TB (70%) were of poor socio-economic class, which restricted their purchase of four FDCs only up to 2-3 months. Only 23% were acquainted with the Pakistan National TB Program (NTP). Except for MDR-TB, the results showed a significant correlation between the experiences of staff with TB awareness. Findings from the quality evaluation of four FDC-TB drugs indicated that the dissolution and content assay of rifampicin were not according to the specifications, and overall, 30% of samples failed to comply

with specifications. However, the other quality attributes were within the limits.
CONCLUSION: In light of the data, it can be concluded that private pharmacies could be crucial to the effective management of NTP through the timely identification of patients with TB, appropriate disease and therapy-related education and counseling, and proper storage and stock maintenance.

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PMCID: PMC10034968
PMID: 36969650 [Indexed for MEDLINE]

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

31. **Factors associated with prevalent Mycobacterium tuberculosis infection and disease among adolescents and adults exposed to rifampin-resistant tuberculosis in the household.**

PLoS One. 2023 Mar 17;18(3):e0283290. doi: 10.1371/journal.pone.0283290. eCollection 2023.

Kim S(1), Hesseling AC(2), Wu X(3), Hughes MD(3), Shah NS(4), Gaikwad S(5), Kumarasamy N(6), Mitchell E(7), Leon M(8), Gonzales P(9), Badal-Faesen S(10), Lourens M(11), Nerette S(12), Shenje J(13), de Koker P(2), Nedsuwan S(14), Mohapi L(15), Chakalisa UA(16), Mngqbisa R(17), Escada RODS(18), Ouma S(19), Heckman B(20), Naini L(21), Gupta A(22), Swindells S(23), Churchyard G(24); ACTG A5300/IMPAACT 2003 PHOENIx Feasibility Study Team.

BACKGROUND: Understanding factors associated with prevalent Mycobacterium tuberculosis infection and prevalent TB disease in household contacts of patients with drug-resistant tuberculosis (TB) may be useful for TB program staff conducting contact investigations.
METHODS: Using data from a cross-sectional study that enrolled index participants with rifampin-resistant pulmonary TB and their household contacts (HHCs), we evaluated HHCs age ≥15 years for factors associated with two outcomes: Mycobacterium tuberculosis infection and TB disease. Among HHCs who were not already diagnosed with current active TB disease by the TB program, Mycobacterium tuberculosis infection was determined by interferon-gamma release assay (IGRA). TB disease was adjudicated centrally. We fitted logistic regression models using generalized estimating equations.

RESULTS: Seven hundred twelve HHCs age ≥15 years enrolled from 279 households in eight high-TB burden countries were a median age of 34 years, 63% female, 22% current smokers and 8% previous smokers, 8% HIV-positive, and 11% previously treated for TB. Of 686 with determinate IGRA results, 471 tested IGRA positive (prevalence 68.8% (95% Confidence Interval: 64.6%, 72.8%)). Multivariable modeling showed IGRA positivity was more common in HHCs aged 25-49 years; reporting prior TB treatment; reporting incarceration, substance use, and/or a period of daily alcohol use in the past 12 months; sharing a sleeping room or more evenings spent with the index participant; living with smokers; or living in a home of materials typical of low socioeconomic status. Forty-six (6.5% (95% Confidence Interval: 4.6%, 9.0%)) HHCs age ≥15 years had prevalent TB disease. Multivariable modeling showed higher prevalence of TB disease among HHCs aged ≥50 years; reporting current or previous smoking; reporting a period of daily alcohol use in the past 12 months; and reporting prior TB treatment. CONCLUSION: We identified overlapping and distinct characteristics associated with Mycobacterium tuberculosis infection and TB disease that may be useful for those conducting household TB investigations.

DOI: 10.1371/journal.pone.0283290
PMCID: PMC10022776
PMID: 36930628 [Indexed for MEDLINE]

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

32. **In-vivo studies on Transitmycin, a potent Mycobacterium tuberculosis inhibitor.**

PLoS One. 2023 Mar 3;18(3):e0282454. doi: 10.1371/journal.pone.0282454. eCollection 2023.

Mondal R(1), Dusthackeer V N A(2), Kannan P(2), Singh AK(3), Thiruvengadam K(2), Manikkam R(4), A S S(2), Balasubramanian M(2), Elango P(2), Ebenezer Rajadas S(2), Bharadwaj D(5), Arumugam GS(6), Ganesan S(6), Kumar A K H(2), Singh M(7), Patil S(3), U C A J(8), Doble M(9), R B(10), Tripathy SP(11), Kumar V(11).

This study involves the in-vitro and in-vivo anti-TB potency and in-vivo safety of Transitmycin (TR) (PubChem CID:90659753)- identified to be a novel secondary metabolite derived from Streptomyces sp (R2). TR was tested in-vitro against

drug resistant TB clinical isolates (n = 49). 94% of DR-TB strains (n = 49) were inhibited by TR at 10μg ml-1. In-vivo safety and efficacy studies showed that 0.005mg kg-1 of TR is toxic to mice, rats and guinea pigs, while 0.001mg kg-1 is safe, infection load did not reduce. TR is a potent DNA intercalator and also targets RecA and methionine aminopeptidases of Mycobacterium. Analogue 47 of TR was designed using in-silico based molecule detoxification approaches and SAR analysis. The multiple targeting nature of the TR brightens the chances of the analogues of TR to be a potent TB therapeutic molecule even though the parental compound is toxic. Analog 47 of TR is proposed to have non-DNA intercalating property and lesser in-vivo toxicity with high functional potency. This study attempts to develop a novel anti-TB molecule from microbial sources. Though the parental compound is toxic, its analogs are designed to be safe through in-silico approaches. However, further laboratory validations on this claim need to be carried out before labelling it as a promising anti-TB molecule.

DOI: 10.1371/journal.pone.0282454
PMCID: PMC9983862
PMID: 36867599 [Indexed for MEDLINE]

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

33. **Circularization of rv0678 for Genotypic Bedaquiline Resistance Testing of Mycobacterium tuberculosis.**

Microbiol Spectr. 2023 Mar 6:e0412722. doi: 10.1128/spectrum.04127-22. Online ahead of print.

Limberis JD(1), Nalyvayko A(1), Ernst JD(1), Metcalfe JZ(2).

Circular DNA offers benefits over linear DNA in diagnostic and field assays, but currently, circular DNA generation is lengthy, inefficient, highly dependent on the length and sequence of DNA, and can result in unwanted chimeras. We present streamlined methods for generating PCR-targeted circular DNA from a 700 bp amplicon of rv0678, the high GC content (65%) gene implicated in Mycobacterium tuberculosis bedaquiline resistance, and demonstrate that these methods work as desired. We employ self-circularization with and without splints, a Gibson cloning-based approach, and novel 2 novel methods for generating pseudocircular

DNA. The circular DNA can be used as a template for rolling circle PCR followed by long-read sequencing, allowing for the error correction of sequence data, and improving the confidence in the drug resistance determination and strain identification; and, ultimately, improving patient treatment. IMPORTANCE Antimicrobial resistance is a global health threat, and drug resistant tuberculosis is a principal cause of antimicrobial resistance-related fatality. The long turnaround time and the need for high containment biological laboratories of phenotypic growth-based Mycobacterium tuberculosis drug susceptibility testing often commit patients to months of ineffective treatment, and there is a groundswell of effort in shifting from phenotypic to sequencing-based genotypic assays. Bedaquiline is a key component to newer, all oral, drug resistant, tuberculosis regimens. Thus, we focus our study on demonstrating the circularization of rv0678, the gene that underlies most M. tuberculosis bedaquiline resistance. We present 2 novel methods for generating pseudocircular DNA. These methods greatly reduce the complexity and time needed to generate circular DNA templates for rolling circle amplification and long-read sequencing, allowing for error correction of sequence data, and improving confidence in the drug resistance determination and strain identification.

DOI: 10.1128/spectrum.04127-22
PMID: 36877083

34. **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).

35. **The evolution of antibiotic resistance is associated with collateral drug phenotypes in Mycobacterium tuberculosis.**

Nat Commun. 2023 Mar 18;14(1):1517. doi: 10.1038/s41467-023-37184-7.

Waller NJE(1)(2), Cheung CY(1), Cook GM(1)(2), McNeil MB(3)(4).

The increasing incidence of drug resistance in Mycobacterium tuberculosis has diminished the efficacy of almost all available antibiotics, complicating efforts to combat the spread of this global health burden. Alongside the development of new drugs, optimised drug combinations are needed to improve treatment success and prevent the further spread of antibiotic resistance. Typically, antibiotic resistance leads to reduced sensitivity, yet in some cases the evolution of drug resistance can lead to enhanced sensitivity to unrelated drugs. This phenomenon of collateral sensitivity is largely unexplored in M. tuberculosis but has the potential to identify alternative therapeutic strategies to combat drug-resistant strains that are unresponsive to current treatments. Here, by using drug susceptibility profiling, genomics and evolutionary studies we provide evidence for the existence of collateral drug sensitivities in an isogenic collection M. tuberculosis drug-resistant strains. Furthermore, in proof-of-concept studies, we demonstrate how collateral drug phenotypes can be exploited to select against and prevent the emergence of drug-resistant strains. This study highlights that the evolution of drug resistance in M. tuberculosis leads to collateral drug responses that can be exploited to design improved drug regimens.

DOI: 10.1038/s41467-023-37184-7
PMCID: PMC10024696
PMID: 36934122 [Indexed for MEDLINE]

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

36. **Berberine governs NOTCH3/AKT signaling to enrich lung-resident memory T cells during tuberculosis.**

PLoS Pathog. 2023 Mar 7;19(3):e1011165. doi: 10.1371/journal.ppat.1011165. eCollection 2023 Mar.

Pahuja I(1)(2), Negi K(1), Kumari A(1), Agarwal M(2), Mukhopadhyay S(1), Mathew B(3), Chaturvedi S(1), Maras JS(3), Bhaskar A(1), Dwivedi VP(1).

Stimulation of naïve T cells during primary infection or vaccination drives the differentiation and expansion of effector and memory T cells that mediate immediate and long-term protection. Despite self-reliant rescue from infection, BCG vaccination, and treatment, long-term memory is rarely established against Mycobacterium tuberculosis (M.tb) resulting in recurrent tuberculosis (TB). Here, we show that berberine (BBR) enhances innate defense mechanisms against M.tb and stimulates the differentiation of Th1/Th17 specific effector memory (TEM), central memory (TCM), and tissue-resident memory (TRM) responses leading to enhanced host protection against drug-sensitive and drug-resistant TB. Through whole proteome analysis of human PBMCs derived from PPD+ healthy individuals, we identify BBR modulated NOTCH3/PTEN/AKT/FOXO1 pathway as the central mechanism of elevated TEM and TRM responses in the human CD4+ T cells. Moreover, BBR-induced glycolysis resulted in enhanced effector functions leading to superior Th1/Th17 responses in human and murine T cells. This regulation of T cell memory by BBR remarkably enhanced the BCG-induced anti-tubercular immunity and lowered the rate of TB recurrence due to relapse and re-infection. These results thus suggest tuning immunological memory as a feasible approach to augment host resistance against TB and unveil BBR as a potential adjunct immunotherapeutic and immunoprophylactic against TB.

DOI: 10.1371/journal.ppat.1011165
PMCID: PMC9990925
PMID: 36881595 [Indexed for MEDLINE]

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

37. **Identification and Quantification of S-Sulfenylation Proteome of Mycobacterium tuberculosis under Oxidative Stress.**

Microbiol Spectr. 2023 Mar 21:e0338622. doi: 10.1128/spectrum.03386-22. Online ahead of print.

Lu Y(1), Chen H(1), Wang P(1), Pang J(1), Lu X(1), Li G(1), Hu X(1), Wang X(1), Yang X(1), Li C(1), Lu Y(#)(2), You X(#)(1).

The ability to maintain redox homeostasis is critical for Mycobacterium tuberculosis (Mtb) to survive the redox stress of the host. There are many antioxidant systems in Mtb to ensure its normal replication and survival in the host, and cysteine thiols are one of them. S-sulfenylation is one of the reversible modifications of cysteine thiols to resist oxidative stress. In the study, we investigated the total cysteine thiols modification and S-sulfenylation modification of Mtb proteome under the oxidative stress provided by hydrogen peroxide. To determine and quantify the S-sulfenylation modified proteins, high specific IodoTMT6plex reagents and high resolution mass spectrometry were used to label and quantify the peptides and proteins modified. There are significant differences for the total cysteine modification levels of 279 proteins and S-sulfenylation modification levels of 297 proteins under hydrogen peroxide stress. Functional enrichment analysis indicated that these cysteine-modified proteins were involved in the oxidation-reduction process, fatty acid biosynthetic process, stress response, protein repair, cell wall, etc. In conclusion, our study provides a view of cysteine modifications of the Mtb proteome under oxidative stress, revealing a series of proteins that may play a role in maintaining redox homeostasis. IMPORTANCE With the continuous spread of drug-resistant tuberculosis, there is an urgent need for new antituberculosis drugs with new mechanisms. The ability of Mtb to resist oxidative stress is extremely important for maintaining redox homeostasis and survival in the host. The reversible modifications of cysteine residues have a dual role of protection from irreversible damage to protein functions and regulation, which plays an important role in the redox homeostasis system. Thus, to discover cysteine modification changes in the proteome level under oxidative stress is quintessential to elucidate its antioxidant mechanism. Our results provided a list of proteins involved in the antioxidant process that potentially could be considered targets for drug discovery and vaccine development. Furthermore, it is the first study to determine and quantify the S-sulfenylation-modified proteins in Mtb, which provided better insight into the Mtb response to the host oxidative defense and enable a deeper understanding of Mtb survival strategies.

DOI: 10.1128/spectrum.03386-22
PMID: 36943050

38. **Inequities between migrants and non-migrants with TB: Surveillance evidence from the Brazilian border State of Roraima.**

One Health. 2022 Dec 9;16:100473. doi: 10.1016/j.onehlt.2022.100473. eCollection 2023 Jun.

de Almeida Soares D(1), Arcêncio RA(2), Fronteira I(1).

INTRODUCTION: Until 2014, there was already a significant burden of TB in Roraima, with this State being among the most affected ones in Brazil. Since 2015, though, there has been a progressive increase in cases of TB in the state of Roraima, with a notorious concentration of cases in Venezuelan migrants. Active international migration in border territories should be seen as a warning signal about the need to strengthen health surveillance and One Health actions that encompass all components involved in the risk of active transmission of diseases as tuberculosis in these scenarios.
OBJECTIVE: This study aims to analyze and compare migrants and non-migrants notified with TB in the State of Roraima in Brazil and identify inequities in terms of diagnosis, access to treatment and outcome of the disease.
STUDY DESIGN: Quantitative, cross-sectional, descriptive study of all confirmed cases of TB notified in the Information System for Notifiable Diseases (SINAN) between 2009 and 2019.
METHODS: Data were described through counts, frequencies, prevalence ratios and 95% confidence interval. We used Poisson regression with robust variance to adjust for confounders.
RESULTS: 2111 cases of TB were reported in Roraima between 2009 and 2019 and in this study (mean age 38.2 ± 18.5 years). Cases were more frequently males, brownish race, indigenous people, with high school level education. 10.9% (n = 181) of TB cases were migrants, mainly from Venezuela (72.9%). Migrants with TB were more prone to be homeless (PR = 3.7). A higher number of cases of readmission after treatment dropout (3.3%) and AIDS diseases (11.2%) was observed among migrants compared to non-migrants. The proportion of DR-TB was higher among migrants. The percent of cure of TB was lower among migrants and the prevalence of abandonment of treatment, transfers and deaths by other causes was higher compared to non-migrants.
CONCLUSIONS: The results of the study have shown considerable differences in the epidemiological profile of TB between migrants and non-migrants living in the State of Roraima, with a tendency for poorer outcomes in the first ones as well as more concentration of vulnerabilities. These results stress out existing inequities between migrants and non-migrants with TB disease and raise questions

on the health care network capacity to address these.

DOI: 10.1016/j.onehlt.2022.100473
PMCID: PMC9791919
PMID: 36578656

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.

39. **Anti-Tuberculosis Mur Inhibitors: Structural Insights and the Way Ahead for Development of Novel Agents.**

Pharmaceuticals (Basel). 2023 Mar 1;16(3):377. doi: 10.3390/ph16030377.

Mehta K(1), Khambete M(1), Abhyankar A(1), Omri A(2).

Mur enzymes serve as critical molecular devices for the synthesis of UDP-MurNAc-pentapeptide, the main building block of bacterial peptidoglycan polymer. These enzymes have been extensively studied for bacterial pathogens such as Escherichia coli and Staphylococcus aureus. Various selective and mixed Mur inhibitors have been designed and synthesized in the past few years. However, this class of enzymes remains relatively unexplored for Mycobacterium tuberculosis (Mtb), and thus offers a promising approach for drug design to overcome the challenges of battling this global pandemic. This review aims to explore the potential of Mur enzymes of Mtb by systematically scrutinizing the structural aspects of various reported bacterial inhibitors and implications concerning their activity. Diverse chemical scaffolds such as thiazolidinones, pyrazole, thiazole, etc., as well as natural compounds and repurposed compounds, have been reviewed to understand their in silico interactions with the receptor or their enzyme inhibition potential. The structural diversity and wide array of substituents indicate the scope of the research into developing varied analogs and providing valuable information for the purpose of modifying reported inhibitors of other multidrug-resistant microorganisms. Therefore, this provides an opportunity to expand the arsenal against Mtb and overcome multidrug-resistant tuberculosis.

DOI: 10.3390/ph16030377
PMCID: PMC10058398
PMID: 36986477

40. **Near-field sensor array with 65-GHz CMOS oscillators can rapidly and comprehensively evaluate drug susceptibility of Mycobacterium.**

Sci Rep. 2023 Mar 7;13(1):3825. doi: 10.1038/s41598-023-30873-9.

Kikuchi S(#)(1), Yamashige Y(2)(3)(4), Hosoki R(5), Harata M(5)(6), Ogawa Y(#)(7).

Multidrug-resistant tuberculosis (MDR-TB) is a major clinical problem. Because Mycobacterium, the causative agent of tuberculosis, are slow-growing bacteria, it takes 6-8 weeks to complete drug susceptibility testing, and this delay contributes to the development of MDR-TB. Real-time drug resistance monitoring technology would be effective for suppressing the development of MDR-TB. In the electromagnetic frequency from GHz to THz regions, the spectrum of the dielectric response of biological samples has a high dielectric constant owing to the relaxation of the orientation of the overwhelmingly contained water molecule network. By measuring the change in dielectric constant in this frequency band in a micro-liquid culture of Mycobacterium, the growth ability can be detected from the quantitative fluctuation of bulk water. The 65-GHz near-field sensor array enables a real-time assessment of the drug susceptibility and growth ability of Mycobacterium bovis (BCG). We propose the application of this technology as a potential new method for MDR-TB testing.

DOI: 10.1038/s41598-023-30873-9
PMCID: PMC9990582
PMID: 36882499 [Indexed for MEDLINE]

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

41. **Next-Generation Diarylquinolines Improve Sterilizing Activity of Regimens with Pretomanid and the Novel Oxazolidinone TBI-223 in a Mouse Tuberculosis Model.**

Antimicrob Agents Chemother. 2023 Mar 15:e0003523. doi: 10.1128/aac.00035-23. Online ahead of print.

Li SY(1), Converse PJ(1), Betoudji F(1), Lee J(1), Mdluli K(2), Upton A(2)(3), Fotouhi N(2), Nuermberger EL(1).

A regimen comprised of bedaquiline (BDQ, or B), pretomanid, and linezolid (BPaL) is the first oral 6-month regimen approved by the U.S. Food and Drug

Administration and recommended by the World Health Organization for the treatment of extensively drug-resistant tuberculosis. We used a well-established BALB/c mouse model of tuberculosis to evaluate the treatment-shortening potential of replacing bedaquiline with either of two new, more potent diarylquinolines, TBAJ-587 and TBAJ-876, in early clinical trials. We also evaluated the effect of replacing linezolid with a new oxazolidinone, TBI-223, exhibiting a larger safety margin with respect to mitochondrial toxicity in preclinical studies. Replacing bedaquiline with TBAJ-587 at the same 25-mg/kg dose significantly reduced the proportion of mice relapsing after 2 months of treatment, while replacing linezolid with TBI-223 at the same 100-mg/kg dose did not significantly change the proportion of mice relapsing. Replacing linezolid or TBI-223 with sutezolid in combination with TBAJ-587 and pretomanid significantly reduced the proportion of mice relapsing. In combination with pretomanid and TBI-223, TBAJ-876 at 6.25 mg/kg was equipotent to TBAJ-587 at 25 mg/kg. We conclude that replacement of bedaquiline with these more efficacious and potentially safer diarylquinolines and replacement of linezolid with potentially safer and at least as efficacious oxazolidinones in the clinically successful BPaL regimen may lead to superior regimens capable of treating both drug-susceptible and drug-resistant TB more effectively and safely.

DOI: 10.1128/aac.00035-23
PMID: 36920217

42. **Implementation of evidence-based multiple focus integrated intensified TB screening to end TB (EXIT-TB) package in East Africa: a qualitative study.**

BMC Infect Dis. 2023 Mar 14;23(1):161. doi: 10.1186/s12879-023-08069-3.

Isangula K(1)(2), Philbert D(3), Ngari F(3), Ajeme T(4), Kimaro G(3), Yimer G(5), Mnyambwa NP(3)(6), Muttamba W(7)(8), Najjingo I(7), Wilfred A(3), Mshiu J(3), Kirenga B(7), Wandiga S(9), Mmbaga BT(10), Donard F(3), Okelloh D(9), Mtesha B(10), Mohammed H(11), Semvua H(10), Ngocho J(10), Mfinanga S(3), Ngadaya E(3).

INTRODUCTION: Tuberculosis (TB) remains a major cause of morbidity and mortality, especially in sub-Saharan Africa. We qualitatively evaluated the implementation of an Evidence-Based Multiple Focus Integrated Intensified TB Screening package (EXIT-TB) in the East African region, aimed at increasing TB case detection and number of patients receiving care.
OBJECTIVE: We present the accounts of participants from Tanzania, Kenya, Uganda, and Ethiopia regarding the implementation of EXIT-TB, and suggestions for scaling up.

METHODS: A qualitative descriptive design was used to gather insights from purposefully selected healthcare workers, community health workers, and other stakeholders. A total of 27, 13, 14, and 19 in-depth interviews were conducted in Tanzania, Kenya, Uganda, and Ethiopia respectively. Data were transcribed and translated simultaneously and then thematically analysed.
RESULTS: The EXIT-TB project was described to contribute to increased TB case detection, improved detection of Multidrug-resistant TB patients, reduced delays and waiting time for diagnosis, raised the index of TB suspicion, and improved decision-making among HCWs. The attributes of TB case detection were: (i) free X-ray screening services; (ii) integrating TB case-finding activities in other clinics such as Reproductive and Child Health clinics (RCH), and diabetic clinics; (iii), engagement of CHWs, policymakers, and ministry level program managers; (iv) enhanced community awareness and linkage of clients; (v) cooperation between HCWs and CHWs, (vi) improved screening infrastructure, (vii) the adoption of the new simplified screening criteria and (viii) training of implementers. The supply-side challenges encountered ranged from disorganized care, limited space, the COVID-19 pandemic, inadequate human resources, inadequate knowledge and expertise, stock out of supplies, delayed maintenance of equipment, to absence of X-ray and GeneXpert machines in some facilities. The demand side challenges ranged from delayed care seeking, inadequate awareness, negative beliefs, fears towards screening, to financial challenges. Suggestions for scaling up ranged from improving service delivery, access to diagnostic equipment and supplies, and infrastructure, to addressing client fears and stigma.
CONCLUSION: The EXIT-TB package appears to have contributed towards increasing TB case detection and reducing delays in TB treatment in the study settings. Addressing the challenges identified is needed to maximize the impact of the EXIT-TB intervention.

DOI: 10.1186/s12879-023-08069-3
PMCID: PMC10013287
PMID: 36918800 [Indexed for MEDLINE]

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

43. **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).

44. **Analysis of the Mechanism of Action of Kushen in the Treatment of Tuberculosis Based on Network Pharmacology.**

Altern Ther Health Med. 2023 Mar;29(2):155-161.

Lin M, Zhou H, Li R, Quan LL, Jin Z, Tong XW.

CONTEXT: Drug-resistant tuberculosis (TB), especially multidrug-resistant TB, has continued to increase and pan-drug-resistant TB and even fully drug-resistant TB have emerged, bringing great challenges to the treatment of TB. Development of new, safe, and effective antituberculosis drugs is an urgent need.
OBJECTIVE: The study intended to evaluate the use of the network pharmacology method to comprehensively and systematically analyze the network relationship of Kushen's main components, targets, and signaling pathways, aiming to provide new ideas and clues for an in-depth study of the mechanism of Kushen's main components in the treatment of pulmonary TB.
DESIGN: The research team performed a Network pharmacology analysis.
SETTING: The study took place in the Department of Respiratory and Critical Care Medicine at the Third People's Hospital of Yichang City in Yichang, Hubei, China.
OUTCOME MEASURES: The research team: (1) screened Kushen's active ingredients and related targets using the Traditional Chinese Medicine System Pharmacology (TCMSP) database and analysis platform; (2) used the GeneCards database and the Online Mendelian Inheritance in Man (OMIM) database to search for disease targets, (3) connected the active ingredient's targets to the disease targets to obtain predictive targets for Kushen to act against TB, (4) used the STRING database to construct a protein-protein interaction (PPI) network map, (5) used the Database for Annotation, Visualization and Integrated Discovery (DAVID) to subject the intersecting genes to gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses, and (6) used the TCMSP and Protein Data Bank (PDB) databases to dock the active ingredients with target-protein molecules.
RESULTS: The research team found 45 active ingredients for Kushen and 177 target-protein genes related to active ingredients. The PPI network map of the Kushen-TB targets and found that the top 10 targets of Kushen were: (1) mitogen-activated protein kinase 8 (MAPK8); (2) protein kinase B (AKT1); (3) MAPK1, (4) estrogen receptor 1 (ESR1), (5) rel avian reticuloendotheliosis viral oncogene homolog A (RELA), (6) interleukin-6 (IL6), (7) MYC proto-oncogene, basic helix-loop-helix (bHLH) transcription factor MYC), (8) retinoid X receptor alpha (RXRA), (9) FOS proto-oncogene activator protein 1 (AP-1) transcription factor subunit (FOS), and (10) JUN proto-oncogene AP-1 transcription factor subunit (JUN). The KEGG analysis suggested that Kushen can intervene in TB through the hypoxia-inducible factor 1 (HIF-1) signaling pathway.
CONCLUSIONS: The network pharmacology analysis showed that Kushen's active ingredients can play a role in the treatment of TB through the HIF-1 signaling pathway.

PMID: 36455142 [Indexed for MEDLINE]

45. **Tuberculosis notifications in regional Victoria, Australia: Implications for public health care in a low incidence setting.**

PLoS One. 2023 Mar 21;18(3):e0282884. doi: 10.1371/journal.pone.0282884. eCollection 2023.

Moyo N(1)(2), Tay EL(3), Trauer JM(1)(4), Burke L(1), Jackson J(5)(6), Commons RJ(7)(8), Boyd SC(9), Singh KP(10), Denholm JT(1)(10).

BACKGROUND: Regionality is often a significant factor in tuberculosis (TB) management and outcomes worldwide. A wide range of context-specific factors may influence these differences and change over time. We compared TB treatment in regional and metropolitan areas, considering demographic and temporal trends affecting TB diagnosis and outcomes.
METHODS: Retrospective analyses of data for patients notified with TB in Victoria, Australia, were conducted. The study outcomes were treatment delays and treatment outcomes. Multivariable Cox proportional hazard model analyses were performed to investigate the effect of regionality in the management of TB. Six hundred and eleven (7%) TB patients were notified in regional and 8,163 (93%) in metropolitan areas between 1995 and 2019. Of the 611 cases in the regional cohort, 401 (66%) were overseas-born. Fifty-one percent of the overseas-born patients in regional Victoria developed TB disease within five years of arrival in Australia. Four cases of multidrug-resistant tuberculosis were reported in regional areas, compared to 97 cases in metropolitan areas. A total of 3,238 patients notified from 2012 to 2019 were included in the survival analysis. The time follow-up for patient delay started at symptom onset date, and the event was the presentation to the healthcare centre. For healthcare system delay, follow-up time began at the presentation to the healthcare centre, and the event was commenced on TB treatment. Cases with extrapulmonary TB in regional areas have a non-significantly longer healthcare system delay than patients in metropolitan (median 64 days versus 54 days, AHR = 0.8, 95% CI 0.6-1.0, P = 0.094).
CONCLUSION: Tuberculosis in regional Victoria is common among the overseas-born population, and patients with extrapulmonary TB in regional areas experienced a non-significant minor delay in treatment commencement with no apparent detriment to treatment outcomes. Improving access to LTBI management in regional areas may reduce the burden of TB.

DOI: 10.1371/journal.pone.0282884
PMCID: PMC10030020
PMID: 36943855 [Indexed for MEDLINE]

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

46. **Isolation and Characterization of Anti-Mycobacterial Natural Products from a Petrosia sp. Marine Sponge.**

J Nat Prod. 2023 Mar 24;86(3):574-581. doi: 10.1021/acs.jnatprod.2c01003. Epub 2023 Mar 7.

Khatri Chhetri B(1), Bhanushali R(2), Liang Y(1), Cepeda MR(1), Niradininoco AK(3), Soapi K(3)(4), Wan B(5), Qader M(5), Franzblau SG(5), Kubanek J(1)(6)(2)(7).

Tuberculosis (TB) is a dreadful infectious disease and a leading cause of mortality and morbidity worldwide, second in 2020 only to severe acute respiratory syndrome 2 (SARS-Cov-2). With limited therapeutic options available and a rise in multidrug-resistant tuberculosis cases, it is critical to develop antibiotic drugs that display novel mechanisms of action. Bioactivity-guided fractionation employing an Alamar blue assay for Mycobacterium tuberculosis strain H37Rv led to the isolation of duryne (13) from a marine sponge Petrosia sp. sampled in the Solomon Islands. Additionally, five new strongylophorine meroditerpene analogues (1-5) along with six known strongylophorines (6-12) were isolated from the bioactive fraction and characterized using MS and NMR spectroscopy, although only 13 exhibited antitubercular activity.

DOI: 10.1021/acs.jnatprod.2c01003
PMCID: PMC10043868
PMID: 36881908 [Indexed for MEDLINE]

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

47. **Monitoring the progress achieved towards ending tuberculosis in the European Union/European Economic Area, 2018 to 2021.**

Euro Surveill. 2023 Mar;28(12):2300154. doi: 10.2807/1560-7917.ES.2023.28.12.2300154.

Cristea V(1), Ködmön C(1), Rosales-Klintz S(1), Pharris A(1), van der Werf MJ(1).

We report progress in the European Union/European Economic Area (EU/EEA) towards the Sustainable Development Goal target for tuberculosis (TB) and for the associated global/regional targets. The TB notification rate and the number of TB deaths declined since 2015 but, if current trends continue, the EU/EEA will not reach the 2030 targets. Performance on treatment initiation targets declined sharply during 2020-2021, while the percentage of TB cases with successful treatment outcomes remains low, at 47.9% of the multidrug-resistant TB cases.

DOI: 10.2807/1560-7917.ES.2023.28.12.2300154
PMCID: PMC10037660
PMID: 36951788 [Indexed for MEDLINE]

Conflict of interest statement: Conflict of interest: None declared.

48. **Identification of potential inhibitors of Mycobacterium tuberculosis shikimate kinase: molecular docking, in silico toxicity and in vitro experiments.**

J Comput Aided Mol Des. 2023 Mar;37(3):117-128. doi: 10.1007/s10822-022-00495-w. Epub 2022 Dec 22.

Freitas de Freitas T(1)(2), Roth CD(1), Abbadi BL(1), Hopf FSM(1)(3), Perelló MA(1), de Matos Czeczot A(1)(2), de Souza EV(1)(3), Borsoi AF(1)(2), Machado P(1)(2)(3), Bizarro CV(1)(3), Basso LA(1)(2)(3), Timmers LFSM(4)(5)(6)(7).

Tuberculosis (TB) is one of the main causes of death from a single pathological agent, Mycobacterium tuberculosis (Mtb). In addition, the emergence of drug-resistant TB strains has exacerbated even further the treatment outcome of TB patients. It is thus needed the search for new therapeutic strategies to improve the current treatment and to circumvent the resistance mechanisms of Mtb. The shikimate kinase (SK) is the fifth enzyme of the shikimate pathway, which is essential for the survival of Mtb. The shikimate pathway is absent in humans, thereby indicating SK as an attractive target for the development of anti-TB drugs. In this work, a combination of in silico and in vitro techniques was used to identify potential inhibitors for SK from Mtb (MtSK). All compounds of our in-house database (Centro de Pesquisas em Biologia Molecular e Funcional, CPBMF) were submitted to in silico toxicity analysis to evaluate the risk of hepatotoxicity. Docking experiments were performed to identify the potential inhibitors of MtSK according to the predicted binding energy. In vitro inhibitory activity of MtSK-catalyzed chemical reaction at a single compound concentration was assessed. Minimum inhibitory concentration values for in vitro

growth of pan-sensitive Mtb H37Rv strain were also determined. The mixed approach implemented in this work was able to identify five compounds that inhibit both MtSK and the in vitro growth of Mtb.

DOI: 10.1007/s10822-022-00495-w
PMCID: PMC9772590
PMID: 36547753 [Indexed for MEDLINE]

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

49. **Prevalence and associated factors of delayed sputum smear conversion in patients treated for smear positive pulmonary tuberculosis: A retrospective follow up study in Sabah, Malaysia.**

PLoS One. 2023 Mar 6;18(3):e0282733. doi: 10.1371/journal.pone.0282733. eCollection 2023.

Khor LA(1), A Wahid UNI(1), Ling LL(2), Liansim SMS(3), Oon J(3), Balakrishnan MN(4), Ng WL(5), Cheong AT(6).

INTRODUCTION: Tuberculosis remains a major health problem globally and in Malaysia, particularly in the state of Sabah. Delayed sputum conversion is associated with treatment failure, drug-resistant tuberculosis and mortality. We aimed to determine the prevalence of delayed sputum conversion among smear positive pulmonary tuberculosis (PTB) patients and its associated factors in Sabah, Malaysia.
METHODS: A retrospective follow up study on all patients newly diagnosed with smear positive pulmonary tuberculosis from 2017 to 2019 was conducted at three government health clinics in Sabah, utilizing data from a national electronic tuberculosis database and medical records. Descriptive statistics and binary logistic regression were applied for data analysis. The outcome of the study was the sputum conversion status at the end of the two-month intensive treatment phase with either successful conversion to smear negative or non-conversion.
RESULTS: 374 patients were included in the analysis. Our patients were generally younger than 60 years old with no medical illness and varying proportions of tuberculosis severity as judged by radiographic appearance and sputum bacillary load upon diagnosis. Foreigners constituted 27.8% of our sample. 8.8% (confidence interval: 6.2-12.2) did not convert to smear negative at the end of the intensive phase. Binary logistic regression showed that older patients ≥60 years old (adjusted odds ratio, AOR = 4.303), foreigners (AOR = 3.184) and

patients with higher sputum bacillary load at diagnosis [2+ (AOR = 5.061) and 3+ (AOR = 4.992)] were more likely to have delayed sputum smear conversion. CONCLUSION: The prevalence of delayed sputum conversion in our study was considerably low at 8.8% with age ≥60 years old, foreigners and higher pre-treatment sputum bacillary load associated with delayed conversion. Healthcare providers should take note of these factors and ensure the patients receive proper follow up treatment.

DOI: 10.1371/journal.pone.0282733
PMCID: PMC9987811
PMID: 36877714 [Indexed for MEDLINE]

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

50. **Liquid chromatography-tandem mass spectrometry analysis of delamanid and its metabolite in human cerebrospinal fluid using protein precipitation and on-line solid-phase extraction.**

J Pharm Biomed Anal. 2023 Apr 1;227:115281. doi: 10.1016/j.jpba.2023.115281. Epub 2023 Feb 3.

Mazanhanga MT(1), Joubert A(1), Castel SA(1), van der Merwe M(1), Maartens G(1), Dooley KE(2), Upton CM(3), Wiesner L(4).

The penetration of the antituberculosis drug delamanid into the central nervous system is not established. The distribution of delamanid and its major metabolite, DM-6705, into the cerebrospinal fluid requires investigation. A liquid chromatography-tandem mass spectrometry method for the quantification of delamanid and DM-6705 in human cerebrospinal fluid was developed and validated. The calibration range for both analytes was 0.300 - 30.0 ng/mL. The deuterium-labelled analogue of delamanid (delamanid-d4) and OPC-14714 were used as internal standards for delamanid and DM-6705, respectively. Samples were processed by protein precipitation followed by on-line solid-phase extraction and high-performance liquid chromatography on an Agilent 1260 HPLC system. A Phenomenex Gemini-NX C18 (5.0 µm, 50 mm × 2.0 mm) analytical column was used for on-line solid-phase extraction, and a Waters Xterra MS C18 (5.0 µm, 100 mm × 2.1 mm) analytical column for chromatographic separation using gradient

elution, at a flow rate of 300 µL/min. The total run time was 7.5 min. Analytes were detected by multiple reaction monitoring on an AB Sciex 5500 triple quadrupole mass spectrometer at unit mass resolution, with electrospray ionization in the positive mode. Accuracy and precision were assessed over three independent validation batches. Extraction recoveries were more than 98% and were consistent across the analytical range. Both analytes in CSF exhibited non-specific adsorption to polypropylene tubes. The method was used to analyse cerebrospinal fluid samples from patients with pulmonary tuberculosis in an exploratory pharmacokinetic study.

DOI: 10.1016/j.jpba.2023.115281
PMCID: PMC10023415
PMID: 36739721 [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.

51. **Stable, compounded bedaquiline suspensions to support practical implementation of pediatric dosing in the field.**

Int J Tuberc Lung Dis. 2023 Mar 1;27(3):189-194. doi: 10.5588/ijtld.22.0440.

Taneja R(1), Nahata MC(2), Scarim J(3), Pande PG(1), Scarim A(3), Hoddinott G(4), Fourie CL(5), Jew RK(6), Schaaf HS(4), Garcia-Prats AJ(7), Hesseling AC(4).

BACKGROUND: Bedaquiline (BDQ) tablets are indicated as part of a combination regimen for the treatment of multidrug-resistant TB in adults, adolescents and children. A dispersible tablet formulation is now approved but is not currently available in all settings. The aim of this study was to develop stable extemporaneous liquid formulations of BDQ that can be stored at room temperature or 30°C for several weeks, to support pragmatic pediatric dosing in the field and reduce wastage.METHODS: BDQ tablets were suspended in simple syrup and a sugar-free vehicle. Each 20 mg/mL formulation was stored at room temperature or 30°C for 30 days in amber dispensing bottles. Appearance, BDQ potency, pH and microbial counts were determined on Days 0, 15 and 30.RESULTS: The BDQ potency in both formulations remained at 98-101% of the theoretical concentration for 30 days. The appearance, pH and microbial count of sugar-free formulation did not change during the 30-day storage. The simple syrup formulation was stable for 15

days as microbial growth was observed on Day 30.CONCLUSIONS: BDQ may be prepared in syrup or sugar-free suspensions: syrup suspensions can be stored for 15 days at room temperature and 30C, whereas sugar-free suspensions can be stored for 30 days at room temperature and 30C. This information will support practical BDQ dosing for children in the field.

CONTEXTE : Les comprimés de bédaquiline (BDQ) sont indiqués dans le cadre d'une association thérapeutique pour le traitement de la TB multirésistante chez l'adulte, l'adolescent et l'enfant. Une préparation sous forme de comprimé dispersible est désormais homologuée, mais elle n'est actuellement pas disponible dans tous les contextes. L'objectif de notre étude était de développer des préparations liquides extemporanées stables de BDQ, pouvant se conserver à température ambiante ou à 30°C pendant plusieurs semaines pour favoriser un dosage pédiatrique pragmatique sur le terrain et réduire les gaspillages.
MÉTHODES : Des comprimés de BDQ ont été formulés en suspensions dans une préparation de sirop simple et dans une préparation sans sucre. Chaque préparation de 20 mg/ml a été conservée à température ambiante ou à 30°C pendant 30 jours dans des flacons ambrés. L'apparence, la puissance de la BDQ, le pH et le taux de bactéries ont été déterminés aux Jours 0, 15 et 30.
RÉSULTATS : La puissance de la BDQ dans les deux préparations est restée à 98–101% de la concentration théorique pendant 30 jours. L'apparence, le pH et le taux de bactéries de la préparation sans sucre n'ont pas changé pendant la période de conservation de 30 jours. La préparation sous forme de sirop simple est restée stable pendant 15 jours, mais une croissance bactérienne a été observée au Jour 30.
CONCLUSIONS : La BDQ peut être préparée en suspension dans une préparation de sirop ou une préparation sans sucre et être conservée pendant respectivement 15 et 30 jours à température ambiante ou à 30°C. Cette information favorisera un dosage pédiatrique pratique de la BDQ sur le terrain.

DOI: 10.5588/ijtld.22.0440
PMCID: PMC9983625
PMID: 36855042 [Indexed for MEDLINE]

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

52. **A Series of Spiropyrimidinetriones that Enhances DNA Cleavage Mediated by Mycobacterium tuberculosis Gyrase.**

ACS Infect Dis. 2023 Mar 10;9(3):706-715. doi: 10.1021/acsinfecdis.3c00012. Epub 2023 Feb 20.

Byl JAW(1), Mueller R(2), Bax B(3), Basarab GS(2), Chibale K(2)(4), Osheroff N(1)(5)(6).

The rise in drug-resistant tuberculosis has necessitated the search for alternative antibacterial treatments. Spiropyrimidinetriones (SPTs) represent an important new class of compounds that work through gyrase, the cytotoxic target of fluoroquinolone antibacterials. The present study analyzed the effects of a novel series of SPTs on the DNA cleavage activity of Mycobacterium tuberculosis gyrase. H3D-005722 and related SPTs displayed high activity against gyrase and increased levels of enzyme-mediated double-stranded DNA breaks. The activities of these compounds were similar to those of the fluoroquinolones, moxifloxacin, and ciprofloxacin and greater than that of zoliflodacin, the most clinically advanced SPT. All the SPTs overcame the most common mutations in gyrase associated with fluoroquinolone resistance and, in most cases, were more active against the mutant enzymes than wild-type gyrase. Finally, the compounds displayed low activity against human topoisomerase IIα. These findings support the potential of novel SPT analogues as antitubercular drugs.

DOI: 10.1021/acsinfecdis.3c00012
PMCID: PMC10006343
PMID: 36802491 [Indexed for MEDLINE]

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

53. **A cohort study of post-COVID-19 condition across the Beta, Delta, and Omicron waves in South Africa: 6-month follow-up of hospitalized and nonhospitalized participants.**

Int J Infect Dis. 2023 Mar;128:102-111. doi: 10.1016/j.ijid.2022.12.036. Epub 2022 Dec 29.

Jassat W(1), Mudara C(2), Vika C(2), Welch R(3), Arendse T(3), Dryden M(2), Blumberg L(3), Mayet N(2), Tempia S(4), Parker A(5), Nel J(6), Perumal R(7), Groome MJ(8), Conradie F(9), Ndjeka N(10), Sigfrid L(11), Merson L(11), Cohen C(4).

OBJECTIVES: The study aimed to describe the prevalence of and risk factors for post-COVID-19 condition (PCC).
METHODS: This was a prospective, longitudinal observational cohort study. Hospitalized and nonhospitalized adults were randomly selected to undergo telephone assessment at 1, 3, and 6 months. Participants were assessed using a standardized questionnaire for the evaluation of symptoms and health-related

quality of life. We used negative binomial regression models to determine factors associated with the presence of ≥1 symptoms at 6 months.
RESULTS: A total of 46.7% of hospitalized and 18.5% of nonhospitalized participants experienced ≥1 symptoms at 6 months (P ≤0.001). Among hospitalized people living with HIV, 40.4% had persistent symptoms compared with 47.1% among participants without HIV (P = 0.108). The risk factors for PCC included older age, female sex, non-Black race, presence of a comorbidity, greater number of acute COVID-19 symptoms, hospitalization/COVID-19 severity, and wave period (lower risk of persistent symptoms for the Omicron compared with the Beta wave). There were no associations between self-reported vaccination status with persistent symptoms.
CONCLUSION: The study revealed a high prevalence of persistent symptoms among South African participants at 6 months but decreased risk for PCC among participants infected during the Omicron BA.1 wave. These findings have serious implications for countries with resource-constrained health care systems.

DOI: 10.1016/j.ijid.2022.12.036
PMCID: PMC9800016
PMID: 36587841 [Indexed for MEDLINE]

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

Other Literature

54. **Treatment Strategy for Rifampin-Susceptible Tuberculosis.**

N Engl J Med. 2023 Mar 9;388(10):873-887. doi: 10.1056/NEJMoa2212537. Epub 2023 Feb 20.

Paton NI(1), Cousins C(1), Suresh C(1), Burhan E(1), Chew KL(1), Dalay VB(1), Lu Q(1), Kusmiati T(1), Balanag VM(1), Lee SL(1), Ruslami R(1), Pokharkar Y(1), Djaharuddin I(1), Sugiri JJR(1), Veto RS(1), Sekaggya-Wiltshire C(1), Avihingsanon A(1), Sarin R(1), Papineni P(1), Nunn AJ(1), Crook AM(1); TRUNCATE-TB Trial Team.

Collaborators: Burhan E, Isbaniah F, Dharmawan INIP, Hakiman APA, Afidjati H, Belarosa D, Krisnanda A, Hadi NUA, Hafirain J, Aditia D, Kusmiati T, Soedarsono S, Kusumaningrum D, Yasin R, Panenggak NSR, Kurniawan RD, Rejeki S, Aryanti N, Ruslami R, Santoso P, Larasmanah A, Ihsan N, Gunawan Y, Sumargo S, Yunivita V, Djaharuddin I, Muis E, Lihawa N, Massi N, Majid Y, Siti Kahfiah Mukhlis A,

Nurjaya I, Lacante SA, Sugiri JJR, Sasmika Suwandi G, Kurniawan K, Santony S, Liem H, Effendi TO, Kristiani M, Rini NM, Aphridasari J, Kurniawan S, Astarini D, Soebroto L, Sulistyowati T, Rasita Y, Rukmana A, Sangsayunh P, Sanchat T, Pingsusaen P, Cheewakul K, Bureechai S, Thuansuwan W, Boonyasopun J, Sangkaew K, Rattanawai S, Avihingsanon A, Gatechompol S, Lwin HMS, Han WM, Ureaphongsukkit T, Chaiyahong P, Suriya P, Ubolyam S, Uanithirat A, Mahanontharit A, Lertarrom P, Jirajariyavej S, Kanokdeeseerat S, Wongwutcharajirakul K, Dalay VB, Golla MMI, Gutierrez EA, Partosa ML, Bayas GV, Wagayen CG, Gelina DB, Garcia ES, Pabruada AG, Perlas LR, Balanag VM Jr, Donato NA, Rivera KCR, Villajuan PCM, Del Rosario ZZ, Tupasi TE, Veto RGMS, Rejaba Baliwagan MB, Balane GI, Geronimo AA, Dela Cruz EMB, Guardiario AM, Villamor MPP, Sarcauga Chua MB, Dela Torre Blanco P, Cagwin RML, Antipuesto Camus K, Sarin R, Saini JK, Sethi P, Tomar M, Bhalla M, Arti S, Bisht SS, Sekaggya-Wiltshire C, Nabisere RM, Otaalo B, Asienzo J, Najjemba L, Nampala J, Alinaitwe L, Kaguiri E, Kityo C, Mugerwa H, Serumaga TA, Masaba T, Najjuuko T, Akol J, Kayiza C, Lugemwa A, Musumba S, Yawe I, Katusiime A, Tumusiime B, Kasozi M, Sula M, Ankunda R, Paton N, Cousins C, Suresh C, Ng NK, Lur EWY, Munawara S, Fanusi F, Cross G, Panchalingham A, Yau G, Papineni P, Rutkute K, Gurumurthy M, Yoong P, Chew KL, Permata Sari I, Lu QS, Lee SL, Gandhi M, Pokharkar Y, Moorakonda RB, Cheung YB, Crook A, Sanders K, Phillips P, Nunn A, Phelan J, Hibberd M, Aprillia C, Rachmawati A, Esconde LMM, Austria B, Pussadee K, Prushyapornsri H, Mungklang P, Janpanich C, Wilmot S, Bedi T, Abubakar I, Davies G, Gilks C, Pandey S, Bin Abdul Muttalif AR, Parajuli BK, Sangsuk K, Balanag V, Thwaites G, Law M, Caoili J, Van Crevel R.

BACKGROUND: Tuberculosis is usually treated with a 6-month rifampin-based regimen. Whether a strategy involving shorter initial treatment may lead to similar outcomes is unclear.
METHODS: In this adaptive, open-label, noninferiority trial, we randomly assigned participants with rifampin-susceptible pulmonary tuberculosis to undergo either standard treatment (rifampin and isoniazid for 24 weeks with pyrazinamide and ethambutol for the first 8 weeks) or a strategy involving initial treatment with an 8-week regimen, extended treatment for persistent clinical disease, monitoring after treatment, and retreatment for relapse. There were four strategy groups with different initial regimens; noninferiority was assessed in the two strategy groups with complete enrollment, which had initial regimens of high-dose rifampin-linezolid and bedaquiline-linezolid (each with isoniazid, pyrazinamide, and ethambutol). The primary outcome was a composite of death, ongoing treatment, or active disease at week 96. The noninferiority margin was 12 percentage points.
RESULTS: Of the 674 participants in the intention-to-treat population, 4 (0.6%) withdrew consent or were lost to follow-up. A primary-outcome event occurred in 7 of the 181 participants (3.9%) in the standard-treatment group, as compared with 21 of the 184 participants (11.4%) in the strategy group with an initial rifampin-linezolid regimen (adjusted difference, 7.4 percentage points; 97.5%

confidence interval [CI], 1.7 to 13.2; noninferiority not met) and 11 of the 189 participants (5.8%) in the strategy group with an initial bedaquiline-linezolid regimen (adjusted difference, 0.8 percentage points; 97.5% CI, -3.4 to 5.1; noninferiority met). The mean total duration of treatment was 180 days in the standard-treatment group, 106 days in the rifampin-linezolid strategy group, and 85 days in the bedaquiline-linezolid strategy group. The incidences of grade 3 or 4 adverse events and serious adverse events were similar in the three groups. CONCLUSIONS: A strategy involving initial treatment with an 8-week bedaquiline-linezolid regimen was noninferior to standard treatment for tuberculosis with respect to clinical outcomes. The strategy was associated with a shorter total duration of treatment and with no evident safety concerns. (Funded by the Singapore National Medical Research Council and others; TRUNCATE-TB ClinicalTrials.gov number, NCT03474198.).

DOI: 10.1056/NEJMoa2212537
PMID: 36808186 [Indexed for MEDLINE]

55. **Tuberculosis and malnutrition: The European perspective.**

Clin Nutr. 2023 Apr;42(4):486-492. doi: 10.1016/j.clnu.2023.01.016. Epub 2023 Feb 10.

Ockenga J(1), Fuhse K(2), Chatterjee S(3), Malykh R(4), Rippin H(5), Pirlich M(6), Yedilbayev A(7), Wickramasinghe K(8), Barazzoni R(9).

Tuberculosis (TB) is a leading infectious cause of death worldwide, despite ongoing efforts to limit its incidence and mortality. Although the European Region has made gains in TB incidence and mortality, it now contends with increasing numbers of multidrug- and rifampicin-resistant tuberculosis (MDR/RR-TB). Malnutrition is a major contributor to the burden of TB and may also be directly caused or enhanced by the onset of TB. The presence of malnutrition may worsen TB and MDR/RR-TB related treatment outcomes and contribute to growing TB drug-resistance. Preventing and treating all forms of malnutrition is an important tool to limit the spread of TB worldwide and improve TB outcomes and treatment efficacy. We carried out a scoping review of the existing evidence that addresses malnutrition in the context of TB. Our review found malnutrition increased the risk of developing TB in high-burden settings and increased the likelihood of developing unfavorable treatment outcomes, including treatment failure, loss to follow-up, and death. The potential impact of nutritional care and improved nutritional status on patient prognosis was more difficult to evaluate due to heterogeneity of patient

populations, treatment protocols, and treatment durations and goals. High-quality trials that consider malnutrition as a major risk factor and relevant treatment target when designing effective strategies to limit TB spread and mortality are needed to inform evidence-based practice. In TB patients, we suggest that widespread and regular nutritional screening, assessment, and counselling, has the potential to increase effectiveness of TB management strategies and improve patient quality of life, overall outcomes, and survival.

DOI: 10.1016/j.clnu.2023.01.016
PMID: 36857957 [Indexed for MEDLINE]

56. **What's new in childhood tuberculosis.**

Curr Opin Pediatr. 2023 Apr 1;35(2):166-175. doi: 10.1097/MOP.0000000000001226. Epub 2023 Feb 7.

Finlayson H(1), Lishman J(1), Palmer M(2).

PURPOSE OF REVIEW: The current review identifies recent advances in the prevention, diagnosis, and treatment of childhood tuberculosis (TB) with a focus on the WHO's updated TB management guidelines released in 2022.
RECENT FINDINGS: The COVID-19 pandemic negatively affected global TB control due to the diversion of healthcare resources and decreased patient care-seeking behaviour. Despite this, key advances in childhood TB management have continued. The WHO now recommends shorter rifamycin-based regimens for TB preventive treatment as well as shorter regimens for the treatment of both drug-susceptible and drug-resistant TB. The Xpert Ultra assay is now recommended as the initial diagnostic test for TB in children with presumed TB and can also be used on stool samples. Point-of-care urinary lipoarabinomannan assays are promising as 'rule-in' tests for children with presumed TB living with HIV. Treatment decision algorithms can be used to diagnose TB in symptomatic children in settings with and without access to chest X-rays; bacteriological confirmation should always be attempted.
SUMMARY: Recent guideline updates are a key milestone in the management of childhood TB, and the paediatric TB community should now prioritize their efficient implementation in high TB burden countries while generating evidence to close current evidence gaps.

DOI: 10.1097/MOP.0000000000001226

PMID: 36749063 [Indexed for MEDLINE]

57. **Update of drug-resistant tuberculosis treatment guidelines: A turning point.**

Int J Infect Dis. 2023 Mar 12:S1201-9712(23)00089-9. doi: 10.1016/j.ijid.2023.03.013. Online ahead of print.

Vanino E(1), Granozzi B(2), Akkerman OW(3), Munoz-Torrico M(4), Palmieri F(5), Seaworth B(6), Tiberi S(7), Tadolini M(8).

In December 2022 World Health Organization released a new treatment for multidrug-resistant/rifampicin-resistant tuberculosis (MDR/RR-TB) guideline. The main novelty of this update is two new recommendations (i) a 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid (600 mg), and moxifloxacin (BPaLM) is recommended in place of the 9-month or longer (18-month) regimens in MDR/RR-TB patients, now including extensive pulmonary TB and extrapulmonary TB (except TB involving central nervous system, miliary TB and osteoarticular TB); (ii) the use of the 9-month all-oral regimen rather than longer (18-months) regimen is suggested in patients with MDR/RR-TB and in whom resistance to fluoroquinolones has been excluded. Longer (18-month) treatments remain a valid option in all cases in which shorter regimens cannot be implemented due to intolerance, drug-drug interactions, extensively drug-resistant tuberculosis, extensive forms of extrapulmonary TB, or previous failure. The new guidelines represent a milestone in MDR/RR-TB treatment landscape, setting the basis for a shorter, all-oral, more acceptable, equitable, and patient-centered model for MDR/RR-TB management. However, some challenges remain to be addressed to allow full implementation of the new recommendations.

DOI: 10.1016/j.ijid.2023.03.013
PMID: 36918080

Conflict of interest statement: Declaration of competing interests Tiberi S. is an employee of GSK, all opinions are his own and not that of the company. All other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

58. **A host blood transcriptional signature differentiates multi-drug/rifampin-resistant tuberculosis (MDR/RR-TB) from drug susceptible**

tuberculosis: a pilot study.

Mol Biol Rep. 2023 Apr;50(4):3935-3943. doi: 10.1007/s11033-023-08307-6. Epub 2023 Feb 7.

Madamarandawala P(1), Rajapakse S(2), Gunasena B(3), Madegedara D(4), Magana-Arachchi D(5).

BACKGROUND: Tuberculosis (TB), caused by the bacterium Mycobacterium tuberculosis is one of the top thirteen causes of death worldwide. The major challenge to control TB is the emergence of drug-resistant tuberculosis (DR-TB); specifically, multi-drug resistant TB which are resistant to the most potent drugs; rifampin and isoniazid. Owing to the inconsistencies of the current diagnostic methods, a single test cannot identify the whole spectrum of DR-TB associated mutations. Recently, host blood transcriptomics has gained attention as a promising technique that develops disease-specific RNA signatures/biomarkers. However, studies on host transcriptomics infected with DR-TB is limited. Herein, we intended to identify genes/pathways that are differentially expressed in multi-drug/rifampin resistant TB (MDR/RR-TB) in contrast to drug susceptible TB.
METHOD AND RESULTS: We conducted blood RNA sequencing of 10 pulmonary TB patients (4; drug susceptible and 6; DR-TB) and 55 genes that were differentially expressed in MDR/RR-TB from drug-susceptible/mono-resistant TB were identified. CD300LD, MYL9, VAMP5, CARD17, CLEC2B, GBP6, BATF2, ETV7, IFI27 and FCGR1CP were found to be upregulated in MDR/RR-TB in all comparisons, among which CLEC2B and CD300LD were not previously linked to TB. In comparison pathway analysis, interferon alpha/gamma response was upregulated while Wnt/beta catenin signaling, lysosome, microtubule nucleation and notch signaling were downregulated.
CONCLUSION: Up/down-regulation of immunity related genes/pathways speculate the collective effect of hosts' attempt to fight against continuously multiplying DR-TB bacteria and the bacterial factors to fight against the host defense. The identified genes/pathways could act as MDR/RR-TB biomarkers, hence, further research on their clinical use should be encouraged.

DOI: 10.1007/s11033-023-08307-6
PMID: 36749527 [Indexed for MEDLINE]

59. **Clinical implications of molecular drug resistance testing for Mycobacterium tuberculosis: a 2023 TBnet/RESIST-TB consensus statement.**

Lancet Infect Dis. 2023 Apr;23(4):e122-e137. doi: 10.1016/S1473-3099(22)00875-1. Epub 2023 Feb 28.

Domínguez J(1), Boeree MJ(2), Cambau E(3), Chesov D(4), Conradie F(5), Cox V(6), Dheda K(7), Dudnyk A(8), Farhat MR(9), Gagneux S(10), Grobusch MP(11), Gröschel MI(12), Guglielmetti L(13), Kontsevaya I(14), Lange B(15), van Leth F(16), Lienhardt C(17), Mandalakas AM(18), Maurer FP(19), Merker M(20), Miotto P(21), Molina-Moya B(22), Morel F(13), Niemann S(23), Veziris N(13), Whitelaw A(24), Horsburgh CR Jr(25), Lange C(18); TBnet and RESIST-TB networks.

Collaborators: Domínguez J, Boeree MJ, Cambau E, Chesov D, Conradie F, Cox V, Dheda K, Dudnyk A, Farhat MR, Gagneux S, Grobusch MP, Gröschel MI, Guglielmetti L, Kontsevaya I, Lange B, van Leth F, Lienhardt C, Mandalakas AM, Maurer F, Merker M, Miotto P, Molina-Moya B, Morel F, Niemann S, Veziris N, Whitelaw A, Horsburgh CR, Lange C.

Drug-resistant tuberculosis is a substantial health-care concern worldwide. Despite culture-based methods being considered the gold standard for drug susceptibility testing, molecular methods provide rapid information about the Mycobacterium tuberculosis mutations associated with resistance to anti-tuberculosis drugs. This consensus document was developed on the basis of a comprehensive literature search, by the TBnet and RESIST-TB networks, about reporting standards for the clinical use of molecular drug susceptibility testing. Review and the search for evidence included hand-searching journals and searching electronic databases. The panel identified studies that linked mutations in genomic regions of M tuberculosis with treatment outcome data. Implementation of molecular testing for the prediction of drug resistance in M tuberculosis is key. Detection of mutations in clinical isolates has implications for the clinical management of patients with multidrug-resistant or rifampicin-resistant tuberculosis, especially in situations when phenotypic drug susceptibility testing is not available. A multidisciplinary team including clinicians, microbiologists, and laboratory scientists reached a consensus on key questions relevant to molecular prediction of drug susceptibility or resistance to M tuberculosis, and their implications for clinical practice. This consensus document should help clinicians in the management of patients with tuberculosis, providing guidance for the design of treatment regimens and optimising outcomes.

DOI: 10.1016/S1473-3099(22)00875-1
PMID: 36868253 [Indexed for MEDLINE]

Conflict of interest statement: Declaration of interests JD reports a technology

licence to GenID (Germany), and honoraria for lectures from Oxford Immunotec (UK). EC reports support for attendance, accommodation, and travel for ECCMID 2022, Lisboa from European Society of Clinical Microbiology and Infectious Diseases (ESCMID), for annual ERL-TB net meetings from ERL-TB net (Network of National Reference Centers for Tuberculosis in Europe), and for the annual congress 2022, Bologna, from the European Society for Mycobacteriology; is a member of the Executive committee of ESCMID; and is chair of the subcommittee for antimycobacterial agents of EUCAST (European Committee on Antimicrobial Susceptibility Testing). MRF reports grants or contracts from NIH/NIAID (5R01AI155765 and 5R21AI154089) and consulting fees (paid to them) from FIND. LG is a member (unpaid) of the data safety monitoring board for the XACT-19 clinical trial in University of Cape Town, Cape Town, South Africa, and is co-principal investigator of two phase 3 clinical trials on shorter treatment for MDR-TB (endTB and endTB-Q), funded by Unitaid. BL reports grants or contracts from European Union, German Ministry for Education and Research (BMBF), Kultusministerkonferenz, German Centre for Infection Research, and Helmholtz Association, and unpaid leadership or fiduciary roles for DZIF IAB, DZIF Steering Committee transplant Cohort, and TBnet chair Epidemiology. SN reports support for this manuscript (eg, funding, provision of study materials, medical writing, and article processing charges) from BMBF (German Center for Infection Research), DFG (Excellenz Cluster Precision Medicine in Chronic Inflammation EXC 2167), and Leibniz Science Campus Evolutionary Medicine of the LUNG (EvoLUNG), and consulting fees from Illumina advisory board in 2022. NV reports grants or contracts for a study on bedaquiline from Janssen. CRH reports grants or contracts from NIH/NIAID (R01AI134430, DAA3-19-65672, R01AI147316 U01AI152980, and R01AI146555), and Centers for Disease Control and Prevention (NU38PS004651); consulting fees from Otsuka Pharmaceuticals; participation on a data safety monitoring board for SODUCU (PanACEA Sutezolid Dose-finding and Combination Evaluation), BEAT-Tuberculosis (Building Evidence for Advancing New treatment for tuberculosis), DECODE (PanACEA Delpazolid Dose-finding and Combination Development), and Médecins Sans Frontières; and a leadership or fiduciary role from the International Union Against Tuberculosis and Lung Diseases. CLa reports support for the present manuscript (eg, funding, provision of study materials, medical writing, and article processing charges) from DZIF (German Center of Infection Research); consulting fees from a consultation service to INSMED, a company that produced liposomal amikacin as an inhalative suspension for the treatment of non-tuberculous mycobacteria pulmonary disease (outside of the scope of this work); speakers' honoraria from Insmed, Gilead, and Janssen (all outside of the scope of this work); is a member of the data safety board of trials from Médecins Sans Frontières (outside of the scope of this work); is supported by the German Center for Infection Research (DZIF); and acknowledges funding from the European Commission (anTBiotic EU-H2020 733079, ClicTB EDCTP2 RIA2017T-2030, stool4TB EDCTP2 RIAD2018-2511, and UNITE4TB EU-IMI 101007873). All other authors declare no competing interests.

60. **Myoinositol and methyl stearate increases rifampicin susceptibility among drug-resistant Mycobacterium tuberculosis expressing Rv1819c.**

Chem Biol Drug Des. 2023 Apr;101(4):883-895. doi: 10.1111/cbdd.14197. Epub 2023 Jan 5.

Nirmal CR(1), Rajadas SE(1), Balasubramanian M(1), Mohanvel SK(1), Aathi MS(2), Munishankar S(1), Chilamakuru NB(3), Thiruvenkadam K(1), Pandiya Raj AK(1), Paraman R(4), Dusthackeer A(1).

The alarming increase in multidrug resistance, which includes Bedaquiline and Delamanid, stumbles success in Tuberculosis treatment outcome. Mycobacterium tuberculosis gains resistance to rifampicin, which is one of the less toxic and potent anti-TB drugs, through genetic mutations predominantly besides efflux pump mediated drug resistance. In recent decades, scientific interventions are being carried out to overcome this hurdle using novel approaches to save this drug by combining it with other drugs/molecules or by use of high dose rifampicin. This study reports five small molecules namely Ellagic acid, Methyl Stearate, Myoinositol, Rutin, and Shikimic acid that exhibit synergistic inhibitory activity with rifampicin against resistant TB isolates. In-silico examinations revealed possible blocking of Rv1819c-an ABC transporter efflux pump that was known to confer resistance in M. tuberculosis to rifampicin. The synergistic anti-TB activity was assessed using a drug combination checkerboard assay. Efflux pump inhibition activity of ellagic acid, myoinositol, and methyl stearate was observed through ethidium bromide accumulation assay in the drug-resistant M. tuberculosis clinical strains and recombinant Mycobacterium smegmatis expressing Rv1819c in coherence with the significant reduction in the minimum inhibitory concentration of rifampicin. Cytotoxicity of the active efflux inhibitors was tested using in silico and ex vivo methods. Myoinositol and methyl stearate were completely non-toxic to the hematological and epithelial cells of different organs under ex vivo conditions. Based on these findings, these molecules can be considered for adjunct TB therapy; however, their impact on other drugs of anti-TB regimen needs to be tested.

DOI: 10.1111/cbdd.14197
PMID: 36533863 [Indexed for MEDLINE]

61. **Diagnosing osteo-articular tuberculosis and multidrug resistance using real-time polymerase chain reaction and high-resolution melt-curve analysis.**

J Orthop Res. 2023 Apr;41(4):891-896. doi: 10.1002/jor.25410. Epub 2022 Jul 13.

Sharma K(1), Sharma M(2), Sharma A(3), Dhillon MS(4).

The study evaluated real-time quantitative polymerase chain reaction (qPCR) and high-resolution melt-curve analysis (HRM) for simultaneous diagnosis of osteo-articular tuberculosis (OATB) and drug resistance. Two hundred and fifty synovial fluid and pus specimens (20 confirmed OATB by culture, 130 suspected OATB, and 100 controls) processed in the Department of Medical Microbiology, PGIMER were subjected to qPCR using rpoB, MPB64, and IS6110 genes. All OATB positive specimens were subjected to HRM for detecting resistance to rifampicin and isoniazid. qPCR detected 129/150 OATB cases with a sensitivity of 86% (95% for confirmed and 84.6% for suspected OATB cases) and specificity of 100%. rpoB and MPB64 genes had higher sensitivity than IS6110 (86% vs. 74.6%). HRM reported eight multidrug resistant (MDR), two mono-rifampicin, and five mono-isoniazid resistant cases, all were concordant with gene sequencing. qPCR followed by HRM analysis offer a simple, accurate, and rapid platform for simultaneous detection of OATB and MDR.

DOI: 10.1002/jor.25410
PMID: 35780389 [Indexed for MEDLINE]

62. **MDR-TB in children: are the same therapy options available worldwide?**

Int J Infect Dis. 2023 Mar 19:S1201-9712(23)00100-5. doi: 10.1016/j.ijid.2023.03.023. Online ahead of print.

Buonsenso D(1), Autore G(2), Cusenza F(2), Passadore L(2), Bonanno F(2), Esposito S(3).

The spread of drug-resistant tuberculosis (TB) encouraged the development of new medicines and the reappraisal of old drugs rarely used in recent years. Providing access for children with drug-resistant TB to appropriate treatments is a cornerstone of strategies to reduce the burden of TB worldwide. Aim of this perspective is to describe the availability of child-friendly medicines to treat drug-resistant TB at the global level. We showed that the development of child-friendly formulations of second-line drugs should be encouraged to promote adherence to recommended treatment regimens and consequently to increase the success rate and to prevent the development of additional mycobacterial resistances. This is even more crucial considering the long duration of

anti-tubercular therapies. Importantly, companies and policy-makers are called to more efforts in facilitating their prompt availability in every contest, as drug-resistant pediatric TB is a global medical problem.

DOI: 10.1016/j.ijid.2023.03.023
PMID: 36944381

63. **An Insight into MptpB inhibitors as a Key Strategy to Treat MDR and XDR-Tuberculosis.**

Curr Pharm Des. 2023 Mar 8. doi: 10.2174/1381612829666230308112634. Online ahead of print.

Jain M(1), Gollapudi S(1), Khatik GL(1).

Tuberculosis (TB) is a chronic, air-borne infectious disease caused by Mycobacterium tuberculosis (Mtb), which prominently affects the lungs and usually manifests in other organs. TB is preventable and curable but what makes it challenging is the emergence of resistance to the available treatment options. MDR-continued TB's expansion is one of the world's most pressing and difficult problems. Mtb revives via the reciprocity between mycobacterium and host signalling pathways. Mtb secretes a virulence component called Mycobacterium tuberculosis protein tyrosine phosphatase (MptpB), which helps to survive against host macrophages. It indicates that targeting secreted virulence factors offers more benefits to circumvent the emergence of resistance. Many effective inhibitors of MptpA and MptpB have been discovered, providing a solid foundation for future research and development. Aside from possessing a structurally unique binding site in the Mtb enzyme, MptpB's minimal resemblance to other human phosphatases provides a broad platform for improving selectivity over host PTPs. We believe that addressing several parts of infection processes in the host and bacteria with combination therapy is the greatest way to reduce treatment burden and medication resistance. We have discussed the recent potent, selective, and efficacious MptpB inhibitors, such as natural and marine-based, isoxazole-linked carboxylic acid-based, oxamic acid-based, and lactone-based inhibitors, as potential strategies for treating TB.

DOI: 10.2174/1381612829666230308112634
PMID: 36892024

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

Trop Med Int Health. 2023 Mar 2. doi: 10.1111/tmi.13867. Online ahead of print.

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

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

DOI: 10.1111/tmi.13867
PMID: 36864011

65. **Clinical Evaluation of the XDR-LFC Assay for the Molecular Detection of Isoniazid, Rifampin, Fluoroquinolone, Kanamycin, Capreomycin, and Amikacin Drug Resistance in a Prospective Cohort.**

J Clin Microbiol. 2023 Mar 23;61(3):e0147822. doi: 10.1128/jcm.01478-22. Epub 2023 Feb 9.

Syed RR(#)(1), Catanzaro DG(#)(2), Colman RE(1), Cooney CG(3), Linger Y(3), Kukhtin AV(3), Holmberg RC(3), Norville R(3), Crudu V(4), Ciobanu N(4), Codreanu A(4), Seifert M(1), Hillery N(5), Chiles P(1), Catanzaro A(1), Rodwell TC(1).

While the goal of universal drug susceptibility testing has been a key component of the WHO End TB Strategy, in practice, this remains inaccessible to many. Rapid molecular tests for tuberculosis (TB) and antituberculosis drug resistance could significantly improve access to testing. In this study, we evaluated the accuracy of the Akonni Biosystems XDR-TB (extensively drug-resistant TB) TruArray and lateral-flow-cell (XDR-LFC) assay (Akonni Biosystems, Inc., Frederick, MD, USA), a novel assay that detects mutations in seven genes associated with resistance to antituberculosis drugs: katG, the inhA promoter, and the ahpC promoter for isoniazid; rpoB for rifampin; gyrA for fluoroquinolones; rrs and the eis promoter for kanamycin; and rrs for capreomycin and amikacin. We evaluated assay performance using direct sputum samples from 566 participants recruited in a prospective cohort in Moldova over 2 years. The sensitivity and specificity against the phenotypic reference were both 100% for isoniazid, 99.2% and 97.9% for rifampin, 84.8% and 99.1% for fluoroquinolones, 87.0% and 84.1% for kanamycin, 54.3% and 100% for capreomycin, and 79.2% and 100% for amikacin, respectively. Whole-genome sequencing data for a subsample of 272 isolates showed 95 to 99% concordance with the XDR-LFC-reported suspected mutations. The XDR-LFC assay demonstrated a high level of accuracy for multiple drugs and met the WHO's minimum target product profile criteria for isoniazid and rifampin, while the sensitivity for fluoroquinolones and amikacin fell below target thresholds, likely due to the absence of a gyrB target in the assay. With optimization, the XDR-LFC shows promise as a novel near-patient technology to rapidly diagnose drug-resistant tuberculosis.

DOI: 10.1128/jcm.01478-22
PMCID: PMC10035299
PMID: 36757183 [Indexed for MEDLINE]

Conflict of interest statement: The authors declare a conflict of interest. T.C.R. and R.E.C. receive salary support from the non-profit organization FIND,

the Global Alliance for Diagnostics. T.C.R. and A.C. are co-founders, board members and shareholders of Verus Diagnostics Inc., a company that was founded with the intent of developing diagnostic assays. T.C.R. and A.C. have not received any financial support from Verus Diagnostics. Verus Diagnostics has not supported the development of the assay described in this manuscript in any way, financial or otherwise, nor was it involved in the design, analysis, or implementation of the study. M.S., T.C.R., and A.C. are co-inventors of a provisional patent for University of California, San Diego intellectual property to diagnose tuberculosis from clinical samples (provisional patent number 63/048.989). C.G.C. and A.V.K. are employees of Akonni Biosystems Inc. Y.L. and R.N. have been previously employed by Akonni Biosystems Inc. C.G.C., Y.L., and A.V.K. are Akonni shareholders.

66. **An unusual case of pleural effusion.**

Intern Emerg Med. 2023 Mar 9. doi: 10.1007/s11739-023-03236-5. Online ahead of print.

Della Torre A(1)(2), Di Francesco P(1), Montanelli GA(1), Bolis M(3), Comelli A(3), Ferrarese M(4), Croci GA(5), Tobaldini E(6)(7).

CASE PRESENTATION: A 63-year-old man presented with fever, thoracalgia, weight loss, diffuse lymphadenopathy, and a massive pleural effusion. Extensive laboratory and radiologic investigations for possible autoimmune, infectious, hematologic, and neoplastic conditions all resulted negative. A lymph node biopsy showed a granulomatous necrotizing lymphadenitis, suspicious for tuberculosis. Although mycobacterium tuberculosis (MT) was never isolated and tuberculin skin test resulted negative, diagnosis of extrapulmonary tuberculosis was made and anti-tubercular therapy was started. Despite the strict adherence to 5 months of treatment, he returned to the emergency ward complaining of fever, chest pain and pleural effusion; total-body CT and PET scans demonstrated a progression of new disseminated nodular consolidations.
DIAGNOSTIC WORK-UP: Microscopic and cultural search for MT and other micro-organisms resulted again negative on urine, stool, blood, pleural fluid, and spinal lesion biopsy. We therefore started considering alternative diagnosis for necrotizing granulomatosis, including multidrug-resistant tuberculosis, Wegener granulomatosis, Churg Strauss syndrome, necrobiotic nodules of rheumatoid arthritis, lymphomatoid granulomatosis and Necrotizing Sarcoid Granulomatosis (NSG). Having already rejected other autoimmune, hematological, and neoplastic disorders, NSG resulted the most consistent hypothesis. With an expert we thus re-examined histological specimens that were suggestive for an atypical presentation of sarcoidosis. Steroid therapy was initiated, achieving symptoms improvement.

DISCUSSION: Sarcoidosis is a rare condition that can be challenging to diagnose, due to its variability in clinical presentation, often mimicking alternative conditions like disseminated tuberculosis. A high degree of suspicion and an experienced lab in anatomical pathology are essential for final diagnosis.

DOI: 10.1007/s11739-023-03236-5
PMID: 36890333

67. **Optimizing Moxifloxacin Dose in MDR-TB Participants with or without Efavirenz Coadministration Using Population Pharmacokinetic Modeling.**

Antimicrob Agents Chemother. 2023 Mar 16;67(3):e0142622. doi: 10.1128/aac.01426-22. Epub 2023 Feb 6.

Chirehwa MT(#)(1), Resendiz-Galvan JE(#)(1), Court R(1), De Kock M(2), Wiesner L(1), de Vries N(3), Harding J(4), Gumbo T(5), Warren R(2), Maartens G(1), Denti P(#)(1), McIlleron H(#)(1)(6).

Moxifloxacin is included in some treatment regimens for drug-sensitive tuberculosis (TB) and multidrug-resistant TB (MDR-TB). Aiming to optimize dosing, we described moxifloxacin pharmacokinetic and MIC distribution in participants with MDR-TB. Participants enrolled at two TB hospitals in South Africa underwent intensive pharmacokinetic sampling approximately 1 to 6 weeks after treatment initiation. Plasma drug concentrations and clinical data were analyzed using nonlinear mixed-effects modeling with simulations to evaluate doses for different scenarios. We enrolled 131 participants (54 females), with median age of 35.7 (interquartile range, 28.5 to 43.5) years, median weight of 47 (42.0 to 54.0) kg, and median fat-free mass of 40.1 (32.3 to 44.7) kg; 79 were HIV positive, 29 of whom were on efavirenz-based antiretroviral therapy. Moxifloxacin pharmacokinetics were described with a 2-compartment model, transit absorption, and elimination via a liver compartment. We included allometry based on fat-free mass to estimate disposition parameters. We estimated an oral clearance for a typical patient to be 17.6 L/h. Participants treated with efavirenz had increased clearance, resulting in a 44% reduction in moxifloxacin exposure. Simulations predicted that, even at a median MIC of 0.25 (0.06 to 16) mg/L, the standard daily dose of 400 mg has a low probability of attaining the ratio of the area under the unbound concentration-time curve from 0 to 24 h to the MIC (fAUC0-24)/MIC target of >53, particularly in heavier participants. The high-dose WHO regimen (600 to 800 mg) yielded higher, more balanced exposures across the weight ranges, with better target attainment. When coadministered

with efavirenz, moxifloxacin doses of up to 1,000 mg are needed to match these exposures. The safety of higher moxifloxacin doses in clinical settings should be confirmed.

DOI: 10.1128/aac.01426-22
PMCID: PMC10019313
PMID: 36744891 [Indexed for MEDLINE]

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

68. **World tuberculosis day 2023 - Reflections on the spread of drug-resistant tuberculosis by travellers and reducing risk in forcibly displaced populations.**

Travel Med Infect Dis. 2023 Mar 22:102568. doi: 10.1016/j.tmaid.2023.102568. Online ahead of print.

Rodriguez-Morales AJ(1), Abbara A(2), Ntoumi F(3), Kapata N(4), Mwaba P(5), Yeboah-Manu D(6), Maeurer M(7), Dar O(8), Abubakar I(9), Zumla A(10).

DOI: 10.1016/j.tmaid.2023.102568
PMID: 36963477

69. **Antimicrobial Peptides： A Promising Strategy for Anti-tuberculosis Therapeutics.**

Protein Pept Lett. 2023 Mar 15. doi: 10.2174/0929866530666230315113624. Online ahead of print.

Ning Y(1), Wang L(1)(2), Wang M(1), Meng X(1)(2), Qiao J(1)(2).

The high global burden of tuberculosis (TB) and the increasing emergence of the drug-resistant (DR) strain of Mycobacterium tuberculosis (Mtb) emphasize the urgent need for novel anti-mycobacterial agents. Antimicrobial peptides (AMPs) are small peptides widely existing in a variety of organisms and usually have amphiphilic cationic structures, which have a selective affinity to the negatively charged bacterial cell wall. Besides direct bactericidal mechanisms, including interacting with the bacterial cell membrane and interfering with the biosynthesis of the cell wall, DNA, or protein, some AMPs are involved in the host's innate immunity. AMPs are promising alternative or complementary agents for the treatment of DR-TB, given their various antibacterial mechanisms and low cytotoxicity. A large number of AMPs, synthetic or natural, from human to bacteriophage sources, have displayed potent anti-mycobacterial activity in vitro and in vivo. In this review, we summarized the features, antimycobacterial

activity, and mechanisms of action of the AMPs according to their sources. Although AMPs have not yet met the expectations for clinical application due to their low bioavailabilities, high cost, and difficulties in large-scale production, their potent antimycobacterial activity and action mechanisms, which are different from conventional antibiotics, make them promising antibacterial agents against DR-Mtb in the future.

DOI: 10.2174/0929866530666230315113624
PMID: 36924097

70. **In vitro activity of tetracycline analogs against multidrug-resistant and extensive drug resistance clinical isolates of Mycobacterium tuberculosis.**

Tuberculosis (Edinb). 2023 Mar 11;140:102336. doi: 10.1016/j.tube.2023.102336. Online ahead of print.

Zhang C(1), Ouyang Q(2), Zhou X(1), Huang Y(1), Zeng Y(1), Deng L(1), Lin D(3), Zheng W(4).

BACKGROUND: Multidrug-resistant tuberculosis (MDR-TB) has become a big threaten to global health. The current strategy for treatment of MDR-TB and extensive drug resistant tuberculosis (XDR-TB) is with low efficacy and high side effect. While new drug is fundamental for cure MDR-TB, repurposing the Food and Drug Administration (FDA)-approved drugs represents an alternative soluation with less cost.
METHODS: The activity of 8 tetracycline-class antibiotics against mycobacterium tuberculosis (M.tb) were determined by Minimum Inhibitory Concentration (MIC) in vitro. A transposon M.smeg libraries was generated by using the Harm phage and then used to isolate the conditional growth mutants in doxycycline containing plate. Eleven mutants were isolated and genomic DNAs were extracted using the cetyltrimethyl ammonium bromide (CTAB) method and analyzed by whole genome sequencing.
RESULTS: We found that three of eight drugs efficiently inhibited mycobacteria growth under the peak plasma concentration in the human body. Further tests showed these three tetracycline analogs (demeclocycline, doxycycline and methacycline) had antimicrobial activity against seven clinical isolates, including MDR and XDR strains. Among them, Doxycycline had the lowest MICs in all mycobacteria strains tested in this study. By using a transposon library, we identify the insertion of transposon in two genes, porin and MshA, associatewith the resistant to doxycycline.

CONCLUSIONS: Our findings show that tetracycline analogs such as doxycycline, has bactericidal activity against not only drug sensitive M.tb, but also clinical MDR and XDR strains, provided proof of concept to repurpose doxycycline to fight MDR-TB and XDR-TB. Further investigations are warranted to clarify the underlying mechanism and optimize the strategy in combination with other anti-TB drugs.

DOI: 10.1016/j.tube.2023.102336
PMID: 36963294

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

71. **Decentralized, Integrated Treatment of RR/MDR-TB and HIV Using a Bedaquiline-Based, Short-Course Regimen Is Effective and Associated With Improved HIV Disease Control.**

J Acquir Immune Defic Syndr. 2023 Apr 15;92(5):385-392. doi: 10.1097/QAI.0000000000003150.

Govender T(1), Jham MA(2), Zhang JC(3), Pillay S(4), Pak Y(5), Pillay P(4), Furin J(6), Malenfant J(7), Murphy RA(8)(9).

BACKGROUND: In decentralized sites, with fewer resources and a high prevalence of advanced HIV, the effectiveness of the new short-course, bedaquiline-based regimen for rifampicin-resistant and multidrug-resistant tuberculosis (RR/MDR-TB) is not well-described.
SETTING: Adults with pulmonary RR/MDR-TB initiating the short-course regimen in KwaZulu-Natal, South Africa were prospectively enrolled at a decentralized program that integrated person-centered TB care.
METHODS: In addition to standard of care monitoring, study visits occurred at enrollment and months 1, 2, 4, 6, and 9. Favorable RR/MDR-TB outcome was defined as cure or treatment completion without loss to follow-up, death, or failure by treatment. In patients with HIV, we assessed antiretroviral therapy (ART) uptake, virologic and immunologic outcomes.
RESULTS: Among 57 patients, HIV was present in 73.7% (95% CI: 60.3-84.5), with a median CD4 count of 170 cells/mm 3 (intraquartile range 49-314). A favorable RR/MDR-TB outcome was achieved in 78.9% (CI: 67.1-87.9). Three deaths occurred, all in the setting of baseline advanced HIV and elevated viral load. Overall, 21.1% (95% CI: 12.1-32.9) experienced a severe or life-threatening adverse event, the most common of which was anemia. Among patients with HIV, enrollment

resulted in increased ART uptake by 24% (95% CI: 12.1%-39.4%), a significant improvement from baseline (P = 0.004); virologic suppression during concomitant treatment was observed in 71.4% (n = 30, 95% CI: 55.4-84.3).
CONCLUSION: Decentralized, person-centered care for RR/MDR-TB in patients with HIV using the short-course, bedaquiline-based regimen is effective and safe. In patients with HIV, enrollment led to improved ART use and reassuring virologic outcomes.

DOI: 10.1097/QAI.0000000000003150
PMCID: PMC10006315
PMID: 36729541 [Indexed for MEDLINE]

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

72. **Targeting caseinolytic protease P and its AAA1 chaperone for tuberculosis treatment.**

Drug Discov Today. 2023 Mar;28(3):103508. doi: 10.1016/j.drudis.2023.103508. Epub 2023 Jan 24.

Xu X(1), Zhang L(1), Yang T(2), Qiu Z(1), Bai L(3), Luo Y(4).

Caseinolytic protease P with its AAA1 chaperone, known as Mycobacterium tuberculosis (Mtb)ClpP1P2 proteolytic machinery, maintains protein homeostasis in Mtb cells and is essential for bacterial survival. It is regarded as an important biological target with the potential to address the increasingly serious issue of multidrug-resistant (MDR) TB. Over the past 10 years, many MtbClpP1P2-targeted modulators have been identified and characterized, some of which have shown potent anti-TB activity. In this review, we describe current understanding of the substrates, structure and function of MtbClpP1P2, classify the modulators of this important protein machine into several categories based on their binding subunits or pockets, and discuss their binding details; Such information provides insights for use in candidate drug research and development of TB treatments by targeting MtbClpP1P2 proteolytic machinery.

DOI: 10.1016/j.drudis.2023.103508
PMID: 36706830 [Indexed for MEDLINE]

73. **An overview of mechanism and chemical inhibitors of shikimate kinase.**

J Biomol Struct Dyn. 2023 Mar 28:1-17. doi: 10.1080/07391102.2023.2193985. Online ahead of print.

Chagaleti BK(1), Reddy MBR(1), Saravanan V(1), B S(1), D P(1), Senthil Kumar P(2), Kathiravan MK(3).

Tuberculosis is a highly infectious disease other than HIV/AIDS and it is one of the top ten causes of death worldwide. Resistance development in the bacteria occurs because of genetic alterations, and the molecular insights suggest that the accumulation of mutation in the individual drug target genes is the primary mechanism of multi-drug resistant tuberculosis. Chorismate is an essential structural fragment for the synthesis of aromatic amino acids and synthesized biochemically by a number of bacteria, including Mycobacterium tuberculosis, utilizing the shikimate pathway. This shikimate kinase is the newer possible target for the generation of novel antitubercular drug because this pathway is expressed only in mycobacterium and not in Mammals. The discovery and development of shikimate kinase inhibitors provide an opportunity for the development of novel selective medications. Multiple shikimate kinase inhibitors have been identified via insilico virtual screening and related protein-ligand interactions along with their in-vitro studies. These inhibitors bind to the active site in a similar fashion to shikimate. In the current review, we present an overview of the biology and chemistry of the shikimate kinase protein and its inhibitors, with special emphasis on the various active scaffold against the enzyme. A variety of chemically diversified synthetic scaffolds including Benzothiazoles, Oxadiazoles, Thiobarbiturates, Naphthoquinones, Thiazoleacetonitriles, Hybridized Pyrazolone derivatives, Orthologous biological macromolecule derivatives, Manzamine Alkaloids derivatives, Dipeptide inhibitor, and Chalcones are discussed in detail. These derivatives bind to the specific target appropriately proving their potential ability through different binding interactions and effectively explored as an effective and selective Sk inhibitor.Communicated by Ramaswamy H. Sarma.

DOI: 10.1080/07391102.2023.2193985
PMID: 36974959

74. **Early culture conversion is a poor marker of treatment outcome among people with HIV and drug-resistant TB.**

HIV Med. 2023 Mar;24(3):335-343. doi: 10.1111/hiv.13392. Epub 2022 Aug 22.

Baluku JB(1)(2), Nabwana M(3), Mwanahamisi SB(4), Kansiime G(4), Nuwagira E(4),

Turyahabwe S(5), Kirenga B(2).

OBJECTIVE: Our objective was to determine associations between early (≤2 months) culture conversion (ECC) among people with HIV and drug-resistant tuberculosis (DRTB) in Uganda.
METHODS: This was a countrywide retrospective cohort of people with bacteriologically confirmed DRTB and a positive baseline culture at 16 centres in Uganda between 2013 and 2019. Data were abstracted from treatment files and unit DRTB registers. Monthly sputum cultures were performed using the Lowenstein-Jensen solid medium.
RESULTS: We included 664 people with DRTB and a positive baseline culture, of whom 353 (53.4%) also had HIV. Among those living with HIV, 225 (63.7%) were male and 331 (94.3%) were on antiretroviral therapy. The median month of culture conversion was 2 (interquartile range [IQR] 1-3). ECC was observed among 226 people living with HIV (64.0%; 95% confidence interval [CI] 58.9-68.9). A DRTB treatment regimen of six or more drugs was associated with ECC among people living with HIV (adjusted odds ratio [aOR] 3.82; 95% CI 1.06-13.82; p = 0.041). Cure and overall treatment success was observed among 232 (65.7%) and 269 (76.2%) people living with HIV, respectively. However, ECC was not associated with cure (crude odds ratio [OR] 0.97; 95% CI 0.61-1.54; p = 0.901), death (OR 1.12; 95% CI 0.61-2.29; p = 0.610), or overall treatment success (OR 1.29; 95% CI 0.78-2.13; p = 0.326).
CONCLUSION: The majority of people living with HIV and DRTB achieve ECC. However, ECC does not predict cure, death, or treatment success. Moreover, it may require six or more drugs to achieve ECC. ECC is not an excellent indicator of the effectiveness of DRTB regimens among people living with HIV.

DOI: 10.1111/hiv.13392
PMID: 36054688 [Indexed for MEDLINE]

75. **Updating the WHO target product profile for next-generation Mycobacterium tuberculosis drug susceptibility testing at peripheral centres.**

PLOS Glob Public Health. 2023 Mar 31;3(3):e0001754. doi: 10.1371/journal.pgph.0001754. eCollection 2023.

MacLean EL(1)(2), Miotto P(3), González Angulo L(4), Chiacchiaretta M(3), Walker TM(5), Casenghi M(6), Rodrigues C(7), Rodwell TC(8)(9), Supply P(10), André E(11)(12), Kohli M(8), Ruhwald M(8), Cirillo DM(3), Ismail N(4), Zignol M(4).

There were approximately 10 million tuberculosis (TB) cases in 2020, of which

500,000 were drug-resistant. Only one third of drug-resistant TB cases were diagnosed and enrolled on appropriate treatment, an issue partly driven by a lack of rapid, accurate drug-susceptibility testing (DST) tools deployable in peripheral settings. In 2014, World Health Organization (WHO) published target product profiles (TPPs) which detailed minimal and optimal criteria to address high-priority TB diagnostic needs, including DST. Since then, the TB community's needs have evolved; new treatment regimens, changes in TB definitions, further emergence of drug resistance, technological advances, and changing end-users requirements have necessitated an update. The DST TPP's revision was therefore undertaken by WHO with the Stop TB Partnership New Diagnostics Working Group. We describe the process of updating the TPP for next-generation TB DST for use at peripheral centres, highlight key updates, and discuss guidance regarding technical and operational specifications.

DOI: 10.1371/journal.pgph.0001754
PMID: 37000774

Conflict of interest statement: I have read the journal's policy and the authors of this manuscript have the following competing interests: PS is a consultant for Genoscreen.

76. **Highly Sensitive Detection of Complicated Mutations of Drug Resistance in Mycobacterium tuberculosis Using a Simple, Accurate, Rapid, and Low-Cost Tailored-Design Competitive Wild-Type Blocking Assay.**

Small Methods. 2023 Mar;7(3):e2201322. doi: 10.1002/smtd.202201322. Epub 2023 Jan 22.

Yan M(1), Zhao Z(2), Wu T(3), Liu T(2), Xu G(1), Xu H(1), Ying B(2).

Establishing simple, rapid, and highly sensitive molecular assays is crucial for timely diagnosis and effective treatment of drug-resistant tuberculosis. However, current genotypic drug susceptibility testing (DST) still encounters enormous challenges including lower sensitivity than phenotypic DST and insufficient accuracy. Herein, a simple, low-cost, multiplex real-time polymerase chain reaction-based assay is established to achieve highly sensitive detection of low-abundant mutants through competitive wild-type blocking (COWTB). Analytical performance of the COWTB assay can achieve 1% or even 0.1%

mutants under background of 10 000 wild-type genomes/test. Furthermore, clinical practice feasibility is evaluated to identify resistance to rifampicin (RIF), isoniazid (INH), and streptomycin (SM) on 92 actual clinical samples, its sensitivity is 93.8% for RIF and 100% for INH and SM, and specificity is 100% each for RIF, INH, and SM when using DNA sequencing as the reference standard. In comparison, the sensitivity of reverse dot blotting assay commonly used in clinics is 93.8%, 90.0%, and 84.6%, and the specificity is 96.1%, 98.6%, and 100% for RIF, INH, and SM, respectively. Importantly, the COWTB assay can also be applicable for other drug-resistant mutations and pave a promising detection strategy to fill the gap between phenotypic and genotypic DST for detecting low-abundant drug-resistant M. tuberculosis.

DOI: 10.1002/smtd.202201322
PMID: 36683186 [Indexed for MEDLINE]

77. **Exploring biogenic chalcones as DprE1 inhibitors for antitubercular activity via in silico approach.**

J Mol Model. 2023 Mar 27;29(4):113. doi: 10.1007/s00894-023-05521-8.

Rathod S(1), Chavan P(2), Mahuli D(3), Rochlani S(4), Shinde S(2), Pawar S(2), Choudhari P(5), Dhavale R(6), Mudalkar P(7), Tamboli F(8).

Cases of drug-resistant tuberculosis (TB) have increased worldwide in the last few years, and it is a major threat to global TB control strategies and the human population. Mycobacterium tuberculosis is a common causative agent responsible for increasing cases of TB and as reported by WHO, approximately, 1.5 million death occurred from TB in 2020. Identification of new therapies against drug-resistant TB is an urgent need to be considered primarily. The current investigation aims to find the potential biogenic chalcone against the potential targets of drug-resistant TB via in silico approach. The ligand library of biogenic chalcones was screened against DprE1. Results of molecular docking and in silico ADMET prediction revealed that ZINC000005158606 has lead-like properties against the targeted protein. Pharmacophore modeling was done to identify the pharmacophoric features and their geometric distance present in ZINC000005158606. The binding stability study performed using molecular dynamics (MD) simulation of the DprE1-ZINC000005158606 complex revealed the conformational stability of the complex system over 100 ns with minimum deviation. Further, the in silico anti-TB sensitivity of ZINC000005158606 was found to be higher as compared to the standards against Mycobacterium tuberculosis. The overall in silico investigation indicated the

potential of identified hit to act as a lead molecule against Mycobacterium tuberculosis.

DOI: 10.1007/s00894-023-05521-8
PMID: 36971900 [Indexed for MEDLINE]

78. **[Progress in research of prophylactic therapy in contacts of rifampicin-resistant tuberculosis patients].**

Zhonghua Liu Xing Bing Xue Za Zhi. 2023 Mar 10;44(3):470-476. doi: 10.3760/cma.j.cn112338-20220729-00673.

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

Wang Z(1), Wang WJ(1), Ding XY(2), Lu P(2), Zhu LM(2), Liu Q(2), Lu W(1).

Tuberculosis (TB) prophylactic therapy for latent infection, which can reduce the risk for the development of active TB, is an important measure in TB control. China recommends prophylactic therapy for latent tuberculosis infection (LTBI) in some key populations to reduce the risk for TB. Contacts of patients with multi-drug and rifampicin-resistant TB (MDR/RR-TB) are at high risk for the infection with drug-resistant pathogen, however, no unified prophylactic therapy regimen has been recommended for LTBI due to exposure to MDR/RR-TB patients. This paper summarizes the current MDR/RR-TB prophylactic therapy regimen and its protection effect based on the results of the retrieval of literature, guidelines, expert consensus and technical specifications to provide reference for the prevention and control of LTBI.

Publisher:
对结核潜伏感染者开展预防性治疗可减少感染人群发生结核病的机会，是控制结核病的一项重要措施。我国推荐对部分重点人群的结核潜伏感染者开展预防性治疗，从而减少结核病发病的风险。耐多药/利福平耐药结核病患者接触者感染耐药病原体的风险高，但是目前对于接触耐多药/利福平耐药结核病患者的感染者还没有推荐的预防性治疗方案，本文检索文献、指南、专家共识和技术规范，对目前耐多药/利福平耐药结核病患者接触者预防性治疗方案和保护效果进行综述，为结核潜伏感染防控提供参考依据。.

DOI: 10.3760/cma.j.cn112338-20220729-00673

PMID: 36942344 [Indexed for MEDLINE]

79. **Assessing Pretomanid for Tuberculosis (APT), a Randomized Phase 2 Trial of Pretomanid-Containing Regimens for Drug-Sensitive Tuberculosis: 12-Week Results.**

Am J Respir Crit Care Med. 2023 Apr 1;207(7):929-935. doi: 10.1164/rccm.202208-1475OC.

Dooley KE(1), Hendricks B(2), Gupte N(3), Barnes G(4), Narunsky K(2), Whitelaw C(2), Smit T(2), Ignatius EH(4), Friedman A(2), Dorman SE(5), Dawson R(2); Assessing Pretomanid for Tuberculosis (APT) Study Team.

Comment in
Am J Respir Crit Care Med. 2023 Apr 1;207(7):816-818.

Rationale: Pretomanid is a new nitroimidazole with proven treatment-shortening efficacy in drug-resistant tuberculosis. Pretomanid-rifamycin-pyrazinamide combinations are potent in mice but have not been tested clinically. Rifampicin, but not rifabutin, reduces pretomanid exposures. Objectives: To evaluate the safety and efficacy of regimens containing pretomanid-rifamycin-pyrazinamide among participants with drug-sensitive pulmonary tuberculosis. Methods: A phase 2, 12-week, open-label randomized trial was conducted of isoniazid and pyrazinamide plus 1) pretomanid and rifampicin (arm 1), 2) pretomanid and rifabutin (arm 2), or 3) rifampicin and ethambutol (standard of care; arm 3). Laboratory values of safety and sputum cultures were collected at Weeks 1, 2, 3, 4, 6, 8, 10, and 12. Time to culture conversion on liquid medium was the primary outcome. Measurements and Main Results: Among 157 participants, 125 (80%) had cavitary disease. Median time to liquid culture negativity in the modified intention-to-treat population (n = 150) was 42 (arm 1), 28 (arm 2), and 56 (arm 3) days (P = 0.01) (adjusted hazard ratio for arm 1 vs. arm 3, 1.41 [95% confidence interval (CI), 0.93-2.12; P = 0.10]; adjusted hazard ratio for arm 2 vs. arm 3, 1.89 [95% CI, 1.24-2.87; P = 0.003]). Eight-week liquid culture conversion was 79%, 89%, and 69%, respectively. Grade ≥3 adverse events occurred in 3 of 56 (5%), 5 of 53 (9%), and 2 of 56 (4%) participants. Six participants were withdrawn because of elevated transaminase concentrations (five in arm 2, one in arm 1). There were three serious adverse events (arm 2) and no deaths. Conclusions: Pretomanid enhanced the microbiologic activity of regimens containing a rifamycin and pyrazinamide. Efficacy and hepatic adverse events appeared highest with the pretomanid and rifabutin-containing regimen. Whether this is due to higher pretomanid concentrations merits exploration. Clinical trial registered with www.clinicaltrials.gov (NCT02256696).

DOI: 10.1164/rccm.202208-1475OC

PMID: 36455068

80. **Extended High-Frequency Audiometry for Ototoxicity Monitoring: A Longitudinal Evaluation of Drug-Resistant Tuberculosis Treatment.**

Am J Audiol. 2023 Mar;32(1):70-80. doi: 10.1044/2022_AJA-22-00039. Epub 2022 Dec 9.

Stevenson LJ(1), Biagio-de Jager L(1), Graham MA(2), Swanepoel W(1)(3).

PURPOSE: The aim of this study was to describe extended high-frequency (EHF) pure-tone audiometry monitoring of ototoxicity in a longitudinal treatment program for drug-resistant tuberculosis (DRTB).
METHOD: This was a retrospective record review of longitudinal conventional (0.25-8 kHz) and EHF (9-16 kHz) audiometry for ototoxicity monitoring of DRTB patients undergoing treatment at community-based clinics between 2013 and 2017. Data from 69 patients with an average age of 37.9 years (SD = 11.2, range: 16.0-63.8 years) were included. Patients were assessed by primary health care audiologists (87%) or community health workers (13%) using portable audiological equipment. The average length of time between initial and exit assessments was 84.6 days (SD = 74.2, range: 2-335 days).
RESULTS: EHF ototoxicity of a mild or greater degree of hearing loss (> 25 dB HL in one or both ears across frequencies) was evident in 85.5% of patients' posttreatment, compared with 47.8% of patients across conventional frequencies. EHF audiometry demonstrated an ototoxic shift (American Speech-Language-Hearing Association criteria) in 56.5% of cases compared with 31.9% when only conventional audiometry was considered. Mean hearing deterioration for patients was significant across EHFs (9-16 kHz) bilaterally ($p < .05$). Absent EHF thresholds at the initial assessment, owing to maximum output limits, was a limitation that occurred most frequently at 16 kHz (17.4%, 24/138).
CONCLUSIONS: EHF audiometry is most sensitive for the early detection of ototoxicity and should be included in monitoring programs. Clinical ototoxicity monitoring protocols should consider shortened assessment approaches that target frequencies most sensitive to ototoxicity, including EHFs.
SUPPLEMENTAL MATERIAL: https://doi.org/10.23641/asha.21651242.

DOI: 10.1044/2022_AJA-22-00039
PMID: 36490390 [Indexed for MEDLINE]

81. **Adverse Events Associated With Treatment for Pan-Susceptible Tuberculosis in San Francisco.**

Clin Infect Dis. 2023 Mar 21;76(6):1121-1124. doi: 10.1093/cid/ciac867.

Louie JK(1)(2), Keh C(2), Agraz-Lara R(1), Phillips A(1), Graves S(1).

Of 373 patients treated for drug-susceptible tuberculosis, 35.4% (46.2% aged ≥65 years) developed moderate/severe adverse events that required treatment interruption (34.8%), first-line drug discontinuation (26.2%, primarily pyrazinamide), second-line drug initiation (30.0%), and treatment duration up to 3.8 months longer. More safe and effective options are needed, including for the elderly.

DOI: 10.1093/cid/ciac867
PMID: 36322073 [Indexed for MEDLINE]

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

82. **Designing a Cas9/gRNA-assisted quantitative Real-Time PCR (CARP) assay for identification of point mutations leading to rifampicin resistance in the human pathogen Mycobacterium tuberculosis.**

Gene. 2023 Mar 20;857:147173. doi: 10.1016/j.gene.2023.147173. Epub 2023 Jan 7.

Augustin L(1), Agarwal N(2).

A simple, rapid and low-cost diagnostic test, which can detect both the drug-sensitive and the drug-resistant tuberculosis (TB) cases is the need of the hour. Here, we developed a Cas9/gRNA-assisted quantitative Real-Time PCR (qRT-PCR) (CARP) assay to detect single nucleotide mutations causing drug resistance in the TB pathogen, Mycobacterium tuberculosis (Mtb). Guide RNAs (gRNAs) were designed against S531 and H526 positions in the rifampicin (RIF)-resistance-determining region (RRDR) of the Mtb rpoB gene that exhibit frequent mutations in the RR clinical isolates of Mtb. Conditions were optimised for in vitro Cas9 cleavage such that single nucleotide changes at these positions can be recognised by Cas9/gRNA complex with high sensitivity and 100% specificity. Further estimation of Cas9/gRNA-based cleavage of target DNA by qRT-PCR led to rapid detection of drug-resistant sequences. The newly designed

CARP assay holds a great deal of promise in the diagnosis and prognosis of patients suffering from TB, in a cost-effective manner.

DOI: 10.1016/j.gene.2023.147173
PMID: 36627091 [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.

83. **Risk factors for peripheral neuropathy in patients on linezolid-containing regimens for drug-resistant TB.**

Int J Tuberc Lung Dis. 2023 Mar 1;27(3):232-234. doi: 10.5588/ijtld.22.0423.

Kwon YS(1), Jang JG(2), Lee J(3), Choi KJ(4), Park JE(3).

DOI: 10.5588/ijtld.22.0423
PMID: 36855040 [Indexed for MEDLINE]

84. **Deciphering the mechanism of resistance by novel double mutations in pncA in Mycobacterium tuberculosis using protein structural graphs (PSG) and structural bioinformatic approaches.**

Comput Biol Med. 2023 Mar;154:106599. doi: 10.1016/j.compbiomed.2023.106599. Epub 2023 Jan 28.

Alshabrmi FM(1), Alatawi EA(2).

The evolution of MDR and XDR-TB is a growing concern and public health safety threat around the world. Gene mutations are the prime cause of drug resistance in tuberculosis, however the reports of double mutations further aggravated the situation. Despite the large-scale genomic sequencing and identification of novel mutations, structure investigation of the protein is still required to structurally and functionally characterize these novel mutations to design novel drugs for improved clinical outcome. Hence, we used structural bioinformatics approaches i.e. molecular modeling, residues communication and molecular simulation to understand the impact of novel double S59Y-L85P, D86G-V180F and S104G-V130 M mutation on the structure, function of pncA encoded Pyrazinamidase

(PZase) and resistance of Pyrazinamide (PZA). Our results revealed that these mutations alter the binding paradigm and destabilize the protein to release the drug. Protein commination network (PCN) revealed variations in the hub residues and sub-networks which consequently alter the internal communication and signaling. The region 1-75 demonstrated higher flexibility in the mutant structures and minimal by the wild type which destabilize of the internally arranged beta-sheets which consequently reduce the binding of PZA and potentially Fe ion in the mutants. Hydrogen bonding analysis further validated the findings. The total binding free energy (ΔG) for each complex i.e. wild type -7.46 kcal/mol, S59Y-L85P -5.21 kcal/mol, S104G-V130 M -5.33 kcal/mol while for the D86G-V180F mutant the TBE was calculated to be -6.26 kcal/mol. This further confirms that these mutations reduce the binding energy of PZA for PZase and causes resistance in the effective therapy for TB. The trajectories motion was also observed to be affected by these mutations. In conclusion, these mutations use destabilizing approach to reduce the binding of PZA and causes resistance. These features can be used to design novel structure-based drugs against Tuberculosis.

DOI: 10.1016/j.compbiomed.2023.106599
PMID: 36731361 [Indexed for MEDLINE]

Conflict of interest statement: Declaration of competing interest Authors declare there is no declaration of interest.

85. **Paediatric Multidrug Resistant Tuberculosis Outbreak in a Low Incidence Country: The Need for Better Diagnosic Tools and More Accessible Treatments.**

Arch Bronconeumol. 2023 Mar;59(3):183-185. doi: 10.1016/j.arbres.2022.11.013. Epub 2022 Nov 30.

[Article in English, Spanish]

Arasa Panisello F(1), Soler Febrer B(2), Lima Cordón AMI(2), García López NR(2), Martínez García E(2), Soriano-Arandes A(3).

DOI: 10.1016/j.arbres.2022.11.013
PMID: 36517312 [Indexed for MEDLINE]

86. **Pharmacokinetics and Efficacy of the Benzothiazinone BTZ-043 against Tuberculous Mycobacteria inside Granulomas in the Guinea Pig Model.**

Antimicrob Agents Chemother. 2023 Mar 28:e0143822. doi: 10.1128/aac.01438-22. Online ahead of print.

Eckhardt E(1), Li Y(2), Mamerow S(3), Schinköthe J(4), Sehl-Ewert J(1), Dreisbach J(5)(6), Corleis B(1), Dorhoi A(1), Teifke J(1), Menge C(3), Kloss F(2), Bastian M(1).

Tuberculosis (TB), caused by Mycobacterium tuberculosis, is the world's leading cause of mortality from a single bacterial pathogen. With increasing frequency, emergence of drug-resistant mycobacteria leads to failures of standard TB treatment regimens. Therefore, new anti-TB drugs are urgently required. BTZ-043 belongs to a novel class of nitrobenzothiazinones, which inhibit mycobacterial cell wall formation by covalent binding of an essential cysteine in the catalytic pocket of decaprenylphosphoryl-β-d-ribose oxidase (DprE1). Thus, the compound blocks the formation of decaprenylphosphoryl-β-d-arabinose, a precursor for the synthesis of arabinans. An excellent in vitro efficacy against M. tuberculosis has been demonstrated. Guinea pigs are an important small-animal model to study anti-TB drugs, as they are naturally susceptible to M. tuberculosis and develop human-like granulomas after infection. In the current study, dose-finding experiments were conducted to establish the appropriate oral dose of BTZ-043 for the guinea pig. Subsequently, it could be shown that the active compound was present at high concentrations in Mycobacterium bovis BCG-induced granulomas. To evaluate its therapeutic effect, guinea pigs were subcutaneously infected with virulent M. tuberculosis and treated with BTZ-043 for 4 weeks. BTZ-043-treated guinea pigs had reduced and less necrotic granulomas than vehicle-treated controls. In comparison to the vehicle controls a highly significant reduction of the bacterial burden was observed after BTZ-043 treatment at the site of infection and in the draining lymph node and spleen. Together, these findings indicate that BTZ-043 holds great promise as a new antimycobacterial drug.

DOI: 10.1128/aac.01438-22
PMID: 36975792

87. **India rejects application to extend patent on TB drug bedaquiline.**

BMJ. 2023 Mar 28;380:724. doi: 10.1136/bmj.p724.

Thiagarajan K(1).

Author information:
(1)Madurai, Tamil Nadu, India.

DOI: 10.1136/bmj.p724
PMID: 36977519 [Indexed for MEDLINE]

88. **Mutations in Rv0678 Reduce Susceptibility of Mycobacterium tuberculosis to the DprE1 Inhibitor TBA-7371.**

Antimicrob Agents Chemother. 2023 Mar 16;67(3):e0005223. doi: 10.1128/aac.00052-23. Epub 2023 Feb 14.

Almeida DV(1), Converse PJ(1), Nuermberger EL(1).

Comment on
Antimicrob Agents Chemother. 2022 Sep 20;66(9):e0090422.

DOI: 10.1128/aac.00052-23
PMCID: PMC10019223
PMID: 36786606 [Indexed for MEDLINE]

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

88. **MarR-Dependent Transcriptional Regulation of mmpSL5 Induces Ethionamide Resistance in Mycobacterium abscessus.**

Antimicrob Agents Chemother. 2023 Mar 29:e0135022. doi: 10.1128/aac.01350-22. Online ahead of print.

Rodriguez R(1), Campbell-Kruger N(2), Gonzalez Camba J(2), Berude J(2), Fetterman R(2), Stanley S(2).

Mycobacterium abscessus (Mabs) is an emerging nontuberculosis mycobacterial (NTM) pathogen responsible for a wide variety of respiratory and cutaneous infections that are difficult to treat with standard antibacterial therapy. Mabs has a high degree of both innate and acquired antibiotic resistance to most clinically relevant drugs, including standard anti-mycobacterial agents. Ethionamide (ETH), an inhibitor of mycolic acid biosynthesis, is currently utilized as a second-line agent for treating multidrug-resistant tuberculosis infections. Here, we show that ETH displays activity against clinical strains of Mabs in vitro at concentrations that are >100× lower than other mycolic acid targeting drugs. Using transposon mutagenesis followed by transposon sequencing (Tn-Seq) and whole-genome sequencing of spontaneous ETH-resistant mutants, we identified MAB_2648c as a genetic determinant of ETH sensitivity in Mabs.

MAB_2648c encodes a MarR family transcriptional regulator of the TetR class of regulators. We show that MAB_2648c represses expression of MAB_2649 (mmpS5) and MAB_2650 (mmpL5). Further, we show that derepression of these genes in MAB_2648c mutants confers resistance to ETH, but not other antibiotics. To identify determinants of resistance that may be shared across antibiotics with distinct mechanisms of action, we also performed Tn-Seq during treatment with amikacin and clarithromycin, drugs currently used clinically to treat Mabs. We found very little overlap in genes that modulate the sensitivity of Mabs to all three antibiotics, suggesting a high degree of specificity for resistance mechanisms in this emerging pathogen.

DOI: 10.1128/aac.01350-22
PMID: 36988462