Literature

1. **Transmission of multidrug-resistant tuberculosis in Beijing, China: An epidemiological and genomic analysis.**

Front Public Health. 2022 Nov 4;10:1019198. doi: 10.3389/fpubh.2022.1019198. eCollection 2022.

Yin J(1)(2), Zhang H(3), Gao Z(3), Jiang H(1)(2), Qin L(1)(2), Zhu C(1)(2), Gao Q(4), He X(3), Li W(1)(2).

BACKGROUND: Understanding multidrug-resistant tuberculosis (MDR-TB) transmission patterns is crucial for controlling the disease. We aimed to identify high-risk populations and geographic settings of MDR-TB transmission.
METHODS: We conducted a population-based retrospective study of MDR-TB patients in Beijing from 2018 to 2020, and assessed MDR-TB recent transmission using whole-genome sequencing of isolates. Geospatial analysis was conducted with kernel density estimation. We combined TransPhylo software with epidemiological investigation data to construct transmission networks. Logistic regression analysis was utilized to identify risk factors for recent transmission.
RESULTS: We included 241 MDR-TB patients, of which 146 (60.58%) were available for genomic analysis. Drug resistance prediction showed that resistance to fluoroquinolones (FQs) was as high as 39.74% among new cases. 36 (24.66%) of the 146 MDR strains were grouped into 12 genome clusters, suggesting recent transmission of MDR strains. 44.82% (13/29) of the clustered patients lived in the same residential community, adjacent residential community or the same street as other cases. The inferred transmission chain found a total of 6 transmission events in 3 clusters; of these, 4 transmission events occurred in residential areas and nearby public places. Logistic regression analysis revealed that being aged 25-34 years-old was a risk factor for recent transmission.
CONCLUSIONS: The recent transmission of MDR-TB in Beijing is severe, and residential areas are common sites of transmission; high levels of FQs drug resistance suggest that FQs should be used with caution unless resistance can be ruled out by laboratory testing.

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PMCID: PMC9672842
PMID: 36408017 [Indexed for MEDLINE]

Conflict of interest statement: The authors declare that the research was

conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

2. **Treatment options for children with multi-drug resistant tuberculosis.**

Expert Rev Clin Pharmacol. 2022 Nov 15. doi: 10.1080/17512433.2023.2148653. Online ahead of print.

Bossù G(1), Autore G(1), Bernardi L(1), Buonsenso D(2), Migliori GB(3), Esposito S(1).

INTRODUCTION: According to the latest report from the World Health Organization (WHO), approximately 10.0 million people fell ill with tuberculosis (TB) in 2020, 12% of which were children aged under 15 years. There is very few experience on treatment of multi-drug resistant (MDR)-TB in pediatrics.
AREAS COVERED: The aim of this review is to analyze and summarize therapeutic options available for children experiencing MDR-TB. We also focused on management of MDR-TB prophylaxis.
EXPERT OPINION: The therapeutic management of children with MDR-TB or MDR-TB contacts is complicated by a lack of knowledge, and the fact that many potentially useful drugs are not registered for pediatric use and there are no formulations suitable for children in the first years of life. Furthermore, most of the available drugs are burdened by major adverse events that need to be taken into account, particularly in the case of prolonged therapy. A close follow-up with a standardized timeline and a comprehensive assessment of clinical, laboratory, microbiologic and radiologic data is extremely important in these patients. Due to the complexity of their management, pediatric patients with confirmed or suspected MDR-TB should always be referred to a specialized center.

DOI: 10.1080/17512433.2023.2148653
PMID: 36378271

3. **Costs and import costs of past, present, and future TB drug regimens: a case study for Karakalpakstan, Uzbekistan.**

J Public Health (Oxf). 2022 Nov 23:fdac124. doi: 10.1093/pubmed/fdac124. Online ahead of print.

Kohler S(1)(2), Sitali N(3), Achar J(4), Paul N(1).

BACKGROUND: Tuberculosis (TB) drugs and their import are costly. We assessed how

shorter TB drug regimens, which were non-inferior or superior in recent TB trials, can affect the costs for purchasing and importing TB drugs.
METHODS: We estimated the drug costs and import costs of 39 longer and shorter TB drug regimens using TB drug prices from the Global Drug Facility and import cost estimates for a TB program in Karakalpakstan, Uzbekistan. Drug regimens from recent TB trials were compared with TB drug regimens following present or past World Health Organization recommendations.
RESULTS: We estimated an import cost of $4.19 and a drug cost of $43 per standard 6-month drug-sensitive (DS)-TB regimen. A new 17-week DS-TB regimen from the TBTC Study 31 currently requires more tablets and is more expensive to import ($6.08) and purchase ($233). The TB program can substantially decrease import costs ($2.26-14) and drug costs ($391-2308) per multidrug-resistant (MDR)-TB regimen when using new 6-month or shorter drug regimens from the Nix-TB, NExT, TB PRACTECAL, ZeNix, or BEAT TB trials instead of 9-20-month regimens with import costs of $9.96-507 and drug costs of $354-15 028. For a commonly used 20-month all-oral, bedaquiline-containing MDR-TB regimen, we estimated costs of $41 for drug import and $1773 for drug purchase.
CONCLUSIONS: The implementation of a new and shorter DS-TB regimen may increase the costs for drug purchase and import. The implementation of new and shorter MDR-TB regimens may decrease the costs for drug purchase and/or drug import.

DOI: 10.1093/pubmed/fdac124
PMID: 36418232

4. **Host-Directed Therapies for Tuberculosis.**

Pathogens. 2022 Nov 3;11(11):1291. doi: 10.3390/pathogens11111291.

Jeong EK(1), Lee HJ(2)(3), Jung YJ(1)(2)(3).

Tuberculosis (TB) is one of the leading causes of death worldwide, consistently threatening public health. Conventional tuberculosis treatment requires a long-term treatment regimen and is associated with side effects. The efficacy of antitubercular drugs has decreased with the emergence of drug-resistant TB; therefore, the development of new TB treatment strategies is urgently needed. In this context, we present host-directed therapy (HDT) as an alternative to current tuberculosis therapy. Unlike antitubercular drugs that directly target Mycobacterium tuberculosis (Mtb), the causative agent of TB, HDT is an approach for treating TB that appropriately modulates host immune responses. HDT

primarily aims to enhance the antimicrobial activity of the host in order to control Mtb infection and attenuate excessive inflammation in order to minimize tissue damage. Recently, research based on the repositioning of drugs for use in HDT has been in progress. Based on the overall immune responses against Mtb infection and the immune-evasion mechanisms of Mtb, this review examines the repositioned drugs available for HDT and their mechanisms of action.

DOI: 10.3390/pathogens11111291
PMID: 36365041

5. **Adherence trajectory as an on-treatment risk indicator among drug-resistant TB patients in the Philippines.**

PLoS One. 2022 Nov 8;17(11):e0277078. doi: 10.1371/journal.pone.0277078. eCollection 2022.

Huddart S(1)(2), Geocaniga-Gaviola DM(3), Crowder R(1)(2), Lim AR(3), Lopez E(3), Valdez CL(3), Berger CA(1)(2), Destura R(4), Kato-Maeda M(1)(2), Cattamanchi A(1)(2), Garfin AMC(3).

INTRODUCTION: High levels of treatment adherence are critical for achieving optimal treatment outcomes among patients with tuberculosis (TB), especially for drug-resistant TB (DR TB). Current tools for identifying high-risk non-adherence are insufficient. Here, we apply trajectory analysis to characterize adherence behavior early in DR TB treatment and assess whether these patterns predict treatment outcomes.
METHODS: We conducted a retrospective analysis of Philippines DR TB patients treated between 2013 and 2016. To identify unique patterns of adherence, we performed group-based trajectory modelling on adherence to the first 12 weeks of treatment. We estimated the association of adherence trajectory group with six-month and final treatment outcomes using univariable and multivariable logistic regression. We also estimated and compared the predictive accuracy of adherence trajectory group and a binary adherence threshold for treatment outcomes.
RESULTS: Of 596 patients, 302 (50.7%) had multidrug resistant TB, 11 (1.8%) extremely drug-resistant (XDR) TB, and 283 (47.5%) pre-XDR TB. We identified three distinct adherence trajectories during the first 12 weeks of treatment: a high adherence group (n = 483), a moderate adherence group (n = 93) and a low adherence group (n = 20). Similar patterns were identified at 4 and 8 weeks. Being in the 12-week moderate or low adherence group was associated with unfavorable six-month (adjusted OR [aOR] 3.42, 95% CI 1.90-6.12) and final (aOR 2.71, 95% 1.73-4.30) treatment outcomes. Adherence trajectory group performed similarly to a binary threshold classification for the prediction of final

treatment outcomes (65.9% vs. 65.4% correctly classified), but was more accurate for prediction of six-month treatment outcomes (79.4% vs. 60.0% correctly classified).
CONCLUSIONS: Adherence patterns are strongly predictive of DR TB treatment outcomes. Trajectory-based analyses represent an exciting avenue of research into TB patient adherence behavior seeking to inform interventions which rapidly identify and support patients with high-risk adherence patterns.

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PMCID: PMC9642894
PMID: 36346814 [Indexed for MEDLINE]

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

6. **Sociodemographic and Clinical Factors Associated with Treatment Outcomes for Drug-resistant Tuberculosis.**

Am J Trop Med Hyg. 2022 Oct 31:tpmd220294. doi: 10.4269/ajtmh.22-0294. Online ahead of print.

de Oliveira Jeronymo Neves AC(1), Gomes Dos Santos AP(1), de Medeiros RL(1), de Oliveira Jeronymo AJ(2), Coelho Neves G(2), de Almeida IN(3), Carvalho de Queiroz Mello F(1), Lineu Kritski A(1).

Drug-resistant tuberculosis (DR-TB) continues to be a serious public health problem. The objective of this study was to evaluate the sociodemographic, radiological, clinical, and outcome characteristics and assess the determinants of unfavorable outcomes in DR-TB. The descriptive-analytical study was carried out in a reference outpatient clinic in Rio de Janeiro, Brazil, among DR-TB cases that received treatment between February 2016 and October 2020, using descriptive statistics, χ2 test, and logistic regression multivariate. Of the 148 cases, 12.2% were resistant to rifampicin, 12.2% were resistant to isoniazid, 18.2% were polyresistant, 56.1% multidrug resistant, and 1.3% were extensively drug resistant. Most of the patients were men, aged up to 44 years, with brown or black skin, having up to 8 years of schooling, unemployed or working in the informal economy, and of low income. Presenting with acquired resistance or positive sputum smear microscopy in the diagnosis, taking more

than four drugs, and being unemployed were associated with unfavorable outcomes. Having no income or acquired resistance doubled the chances of unfavorable outcomes. There was a high proportion of unfavorable outcomes, thereby highlighting the need to concentrate efforts on planning and executing public policies that include the severity of DR-TB and its risk factors.

DOI: 10.4269/ajtmh.22-0294
PMID: 36316000

7. **Transmission and Drug Resistance Genotype of Multidrug-Resistant or Rifampicin-Resistant Mycobacterium tuberculosis in Chongqing, China.**

Microbiol Spectr. 2022 Oct 26;10(5):e0240521. doi: 10.1128/spectrum.02405-21. Epub 2022 Oct 10.

Zhao B(#)(1), Liu C(#)(1), Fan J(1), Ma A(1), He W(2), Hu Y(3), Zhao Y(1).

Multidrug-resistant or rifampicin-resistant tuberculosis (MDR/RR-TB) is a global barrier for the Stop TB plan. To identify risk factors for treatment outcome and cluster transmission of MDR/RR-TB, whole-genome sequencing (WGS) data of isolates from patients of the Chongqing Tuberculosis Control Institute were used for phylogenetic classifications, resistance predictions, and cluster analysis. A total of 223 MDR/RR-TB cases were recorded between 1 January 2018 and 31 December 2020. Elderly patients and those with lung cavitation are at increased risk of death due to MDR/RR-TB. A total of 187 MDR/RR strains were obtained from WGS data; 152 were classified as lineage 2 strains. Eighty (42.8%) strains differing by a distance of 12 or fewer single nucleotide polymorphisms were classified as 20 genomic clusters, indicating recent transmission. Patients infected with lineage 2 strains or those with occupations listed as "other" are significantly associated with a transmission cluster of MDR/RR-TB. Analysis of resistant mutations against first-line tuberculosis drugs found that 76 (95.0%) of all 80 strains had the same mutations within each cluster. A total of 55.0% (44 of 80) of the MDR/RR-TB strains accumulated additional drug resistance mutations along the transmission chain, especially against fluoroquinolones (63.6% [28 of 44]). Recent transmission of MDR/RR strains is driving the MDR/RR-TB epidemics, leading to the accumulation of more serious resistance along the transmission chains. IMPORTANCE The drug resistance molecular characteristics of MDR/RR-TB were elucidated by genome-wide analysis, and risk factors for death by MDR/RR-TB were identified in combination with patient information. Cluster characteristics of MDR/RR-TB in the region were analyzed by genome-wide analysis, and risk factors for cluster transmission (recent transmission) were analyzed. These analyses provide reference for the prevention and treatment of MDR/RR-TB in Chongqing.

DOI: 10.1128/spectrum.02405-21
PMCID: PMC9604020
PMID: 36214695 [Indexed for MEDLINE]

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

8. **Drug re-engineering and repurposing: A significant and rapid approach to tuberculosis drug discovery.**

Arch Pharm (Weinheim). 2022 Nov;355(11):e2200214. doi: 10.1002/ardp.202200214. Epub 2022 Jul 15.

Reddy DS(1), Sinha A(1), Kumar A(1), Saini VK(2).

The prevalence of tuberculosis (TB) remains the leading cause of death from a single infectious agent, ranking it above all other contagious diseases. The problem to tackle this disease seems to become even worse due to the outbreak of SARS-CoV-2. Further, the complications related to drug-resistant TB, prolonged treatment regimens, and synergy between TB and HIV are significant drawbacks. There are several drugs to treat TB, but there is still no rapid and accurate treatment available. Intensive research is, therefore, necessary to discover newer molecular analogs that can probably eliminate this disease within a short span. An increase in efficacy can be achieved through re-engineering old TB-drug families and repurposing known drugs. These two approaches have led to the production of newer classes of compounds with novel mechanisms to treat multidrug-resistant strains. With respect to this context, we discuss structural aspects of developing new anti-TB drugs as well as examine advances in TB drug discovery. It was found that the fluoroquinolone, oxazolidinone, and nitroimidazole classes of compounds have greater potential to be further explored for TB drug development. Most of the TB drug candidates in the clinical phase are modified versions of these classes of compounds. Therefore, here we anticipate that modification or repurposing of these classes of compounds has a higher probability to reach the clinical phase of drug development. The information provided will pave the way for researchers to design and identify newer molecular analogs for TB drug development and also broaden the scope of exploring future-generation potent, yet safer anti-TB drugs.

DOI: 10.1002/ardp.202200214
PMID: 35841594 [Indexed for MEDLINE]

9. **Cardiovascular risk factors among people with drug-resistant tuberculosis in Uganda.**

BMC Cardiovasc Disord. 2022 Nov 4;22(1):464. doi: 10.1186/s12872-022-02889-y.

Baluku JB(1)(2)(3), Nabwana M(4), Nalunjogi J(5), Muttamba W(5)(6), Mubangizi I(7), Nakiyingi L(8), Ssengooba W(5)(9), Olum R(10), Bongomin F(11)(12), Andia-Biraro I(8), Worodria W(5)(8).

: Tuberculosis (TB) and its risk factors are independently associated with cardiovascular disease (CVD). We determined the prevalence and associations of CVD risk factors among people with drug-resistant tuberculosis (DRTB) in Uganda.
METHODS: In this cross-sectional study, we enrolled people with microbiologically confirmed DRTB at four treatment sites in Uganda between July to December 2021. The studied CVD risk factors were any history of cigarette smoking, diabetes mellitus (DM) hypertension, high body mass index (BMI), central obesity and dyslipidaemia. We used modified Poisson regression models with robust standard errors to determine factors independently associated with each of dyslipidaemia, hypertension, and central obesity.
RESULTS: Among 212 participants, 118 (55.7%) had HIV. Overall, 196 (92.5%, 95% confidence interval (CI) 88.0-95.3) had ≥ 1 CVD risk factor. The prevalence; 95% CI of individual CVD risk factors was: dyslipidaemia (62.5%; 55.4-69.1), hypertension (40.6%; 33.8-47.9), central obesity (39.3%; 32.9-46.1), smoking (36.3%; 30.1-43.1), high BMI (8.0%; 5.0-12.8) and DM (6.5%; 3.7-11.1). Dyslipidaemia was associated with an increase in glycated haemoglobin (adjusted prevalence ratio (aPR) 1.14, 95%CI 1.06-1.22). Hypertension was associated with rural residence (aPR 1.89, 95% CI 1.14-3.14) and previous history of smoking (aPR 0.46, 95% CI 0.21-0.98). Central obesity was associated with increasing age (aPR 1.02, 95%CI 1.00-1.03), and elevated diastolic blood pressure (aPR 1.03 95%CI 1.00-1.06).
CONCLUSION: There is a high prevalence of CVD risk factors among people with DRTB in Uganda, of which dyslipidaemia is the commonest. We recommend integrated services for identification and management of CVD risk factors in DRTB.

DOI: 10.1186/s12872-022-02889-y
PMCID: PMC9636825
PMID: 36333654 [Indexed for MEDLINE]

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

10. **Efficacy of Tuberculosis Treatment in Patients with Drug-Resistant Tuberculosis with the Use of Bedaquiline: The Experience of the Russian Federation.**

Antibiotics (Basel). 2022 Nov 14;11(11):1622. doi: 10.3390/antibiotics11111622.

Starshinova A(1), Dovgalyk I(2), Belyaeva E(3), Glushkova A(4), Osipov N(5)(6), Kudlay D(7)(8).

In the conditions of the continued growth of multiple- and extensive drug-resistant tuberculosis, use of the new highly effective anti-tuberculosis drugs in this patient category is of great relevance. The aim of the study was determination the efficacy of treatment in patients with multidrug- and extensive drug-resistant tuberculosis using bedaquiline based on studies published in the Russian Federation.
MATERIALS AND METHODS: The authors analyzed data published in studies from 2014 to 2022; 41 publications were included in total and 17 articles corresponded to the study design. The results of treatment of 1404 tuberculosis patients with MDR/XDR TB were described. Bedaquiline was used according to the standard scheme with a description of the treatment results after 24-26 weeks. Treatment efficacy was estimated according to accepted criteria.
RESULTS OF THE STUDY: The analysis showed that the treatment efficacy on conversion was achieved in 79.5% of cases (95% Cl 76.5-82.3), and recovery was observed in 82.0% of cases (95% Cl 78.6-85.1). Departure from the therapy was observed in rare cases (9.8%; 95% Cl 7.9-12.2). Deaths were recorded in 6.5% of cases (95% Cl 4.9-8.3), which were associated with the severe disease and concomitant pathology in 74.3%. The development of adverse events was noted in half of the patients (55.7%); however, bedaquiline cancellation occurred in a few cases (7.0%; 95% Cl 3.0-13.0). From analyzing data in patients with MDR and XDR TB, the efficacy of treatment was 89.9% (95% Cl 85.9-93.2) and 71.9% (95% Cl 66.2-77.1), respectively.
CONCLUSION: Use of bedaquiline in treatment makes it possible to achieve recovery of patients with MDR/XDR TB in 82.0% of cases with patients dropping out of treatment in 9.8%. At the same time, in patients with MDR TB, recovery was achieved in 89.9% of cases, while in patients with XDR TB, 71.9% of cases recovered.

DOI: 10.3390/antibiotics11111622
PMID: 36421267

11. **Characteristics of Drug-sensitive and Drug-resistant Tuberculosis Cases among Adults at Tuberculosis Referral Hospitals in Indonesia.**

Am J Trop Med Hyg. 2022 Oct 17;107(5):984-991. doi: 10.4269/ajtmh.22-0142. Print 2022 Nov 14.

Burhan E(1), Karyana M(2), Karuniawati A(3), Kusmiati T(4), Wibisono BH(5), Handayani D(1), Riyanto BS(6), Sajinadiyasa IGK(7), Sinaga BYM(8), Djaharuddin I(9), Indah Sugiyono R(10), Susanto NH(10), Diana A(10)(11), Kosasih H(10), Lokida D(12); Siswanto(2), Neal A(13), Lau CY(14), Siddiqui S(13).

As Indonesia's rifampin resistance testing rates are lower than global testing rates per the 2020 WHO global tuberculosis (TB) report, prevalence of multidrug-resistant TB may be underestimated. Our study aimed to evaluate prevalence and patterns of TB drug resistance (DR) within Indonesia. We conducted a cross-sectional analysis of baseline data collected from 2017-2018 as part of a cohort study of adults with presumed pulmonary TB at 7 DR-TB referral hospitals in Indonesia. Bacteriological examinations (acid-fast bacilli, GeneXpert, sputum culture) and drug-susceptibility testing were performed following the guidelines of the National TB Program. Of 447 participants with complete bacteriological examinations, 312 (69.8%) had positive sputum cultures for Mycobacterium tuberculosis. The proportion of MDR and pre-extensively drug-resistant was higher in previously treated compared with newly diagnosed participants (52.5% [73/139] versus 15% [26/173]). Compared with drug-sensitive case, drug-resistant TB was associated with cavities. Given the difference between rates of DR in TB referral hospitals from our study compared with the WHO survey in 2019 that showed 17.7% and 3.3% DR among previously treated and newly diagnosed participants globally, further characterization of Indonesia's TB epidemiology in the general population is needed. Strategies, including public policies to optimize case finding, strengthen capacity for resistance testing, and prevent loss to follow-up will be critical to reduce the burden of TB in Indonesia.

DOI: 10.4269/ajtmh.22-0142
PMID: 36252800 [Indexed for MEDLINE]

12. **New Drugs and Regimens for Tuberculosis Disease Treatment in Children and Adolescents.**

J Pediatric Infect Dis Soc. 2022 Oct 31;11(Supplement_3):S101-S109. doi: 10.1093/jpids/piac047.

Garcia-Prats AJ(1)(2), Starke JR(3), Waning B(4), Kaiser B(4), Seddon JA(2)(5).

After almost 30 years of relative stagnation, research over the past decade has led to remarkable advances in the treatment of both drug-susceptible (DS) and

drug-resistant (DR) tuberculosis (TB) disease in children and adolescents. Compared with the previous standard therapy of at least 6 months, 2 new regimens lasting for only 4 months for the treatment of DS-TB have been studied and are recommended by the World Health Organization (WHO), along with a shortened 6-month regimen for treatment of DS-TB meningitis. In addition, the 18- to 24-month regimens previously used for DR-TB that included painful injectable drugs with high rates of adverse effects have been replaced with shorter, safer all-oral regimens. Advances that have improved treatment include development of new TB drugs (bedaquiline, delamanid, pretomanid), reapplication of older TB drugs (rifampicin and rifapentine), and repurposing of other drugs (clofazimine and linezolid). The development of child-friendly formulations for many of these drugs has further enhanced the ability to safely and effectively treat DS- and DR-TB in children and adolescents. The characteristics and use of these drugs, regimens, and formulations are reviewed.

DOI: 10.1093/jpids/piac047
PMID: 36314547 [Indexed for MEDLINE]

13. **Bedaquiline safety, efficacy, utilization and emergence of resistance following treatment of multidrug-resistant tuberculosis patients in South Africa: a retrospective cohort analysis.**

BMC Infect Dis. 2022 Nov 21;22(1):870. doi: 10.1186/s12879-022-07861-x.

Pai H(1), Ndjeka N(2), Mbuagbaw L(3), Kaniga K(4), Birmingham E(5), Mao G(4), Alquier L(5), Davis K(4), Bodard A(6), Williams A(7), Van Tongel M(6), Thoret-Bauchet F(8), Omar SV(9), Bakare N(10).

BACKGROUND: This retrospective cohort study assessed benefits and risks of bedaquiline treatment in multidrug-resistant-tuberculosis (MDR-TB) combination therapy by evaluating safety, effectiveness, drug utilization and emergence of resistance to bedaquiline.
METHODS: Data were extracted from a register of South African drug-resistant-tuberculosis (DR-TB) patients (Electronic DR-TB Register [EDRWeb]) for newly diagnosed patients with MDR-TB (including pre-extensively drug-resistant [XDR]-TB and XDR-TB and excluding rifampicin-mono-resistant [RR]-TB, as these patients are by definition not multidrug-resistant), receiving either a bedaquiline-containing or non-bedaquiline-containing regimen, at 14 sites in South Africa. Total duration of treatment and follow-up was up to

30 months, including 6 months' bedaquiline treatment. WHO treatment outcomes within 6 months after end-of-treatment were assessed in both patient groups. Longer term mortality (up to 30 months from treatment start) was evaluated through matching to the South African National Vital Statistics Register. Multivariable Cox proportional hazards analyses were used to predict association between receiving a bedaquiline-containing regimen and treatment outcome.
RESULTS: Data were extracted from EDRWeb for 5981 MDR-TB patients (N = 3747 bedaquiline-treated; N = 2234 non-bedaquiline-treated) who initiated treatment between 2015 and 2017, of whom 40.7% versus 80.6% had MDR-TB. More bedaquiline-treated than non-bedaquiline-treated patients had pre-XDR-TB (27.7% versus 9.5%) and XDR-TB (31.5% versus 9.9%) per pre-2021 WHO definitions. Most patients with treatment duration data (94.3%) received bedaquiline for 6 months. Treatment success (per pre-2021 WHO definitions) was achieved in 66.9% of bedaquiline-treated and 49.4% of non-bedaquiline-treated patients. Death was reported in fewer bedaquiline-treated (15.4%) than non-bedaquiline-treated (25.6%) patients. Bedaquiline-treated patients had increased likelihood of treatment success and decreased risk of mortality versus non-bedaquiline-treated patients. In patients with evaluable drug susceptibility testing data, 3.5% of bedaquiline-susceptible isolates at baseline acquired phenotypic resistance. Few patients reported bedaquiline-related treatment-emergent adverse events (TEAEs) (1.8%), TEAE-related bedaquiline discontinuations (1.4%) and QTcF values > 500 ms (2.5%) during treatment.
CONCLUSION: Data from this large cohort of South African patients with MDR-TB showed treatment with bedaquiline-containing regimens was associated with survival and effectiveness benefit compared with non-bedaquiline-containing regimens. No new safety signals were detected. These data are consistent with the positive risk-benefit profile of bedaquiline and warrant continued implementation in combination therapy for MDR-TB treatment.

DOI: 10.1186/s12879-022-07861-x
PMID: 36414938 [Indexed for MEDLINE]

14. **Resistance patterns among drug-resistant tuberculosis patients and trends-over-time analysis of national surveillance data in Gabon, Central Africa.**

Infection. 2022 Oct 28:1-8. doi: 10.1007/s15010-022-01941-5. Online ahead of print.

Abdul JBPAA(#)(1), Adegbite BR(#)(2)(3)(4), Ndanga MED(1), Edoa JR(1), Mevyann RC(1), Mfoumbi GRAI(1), de Dieu TJ(5), Mahoumbou J(6), Biyogho CM(1), Jeyaraj

S(7), Niemann S(8), Lell B(1)(5), Kremsner PG(1)(5), Alabi AS(1)(9), Adegnika AA(1)(9)(10)(11), Grobusch MP(12)(13)(14)(15)(16).

OBJECTIVE: Routinely generated surveillance data are important for monitoring the effectiveness of MDR-TB control strategies. Incidence of rifampicin-resistant tuberculosis (RR-TB) is a key indicator for monitoring MDR-TB.
METHODS: In a longitudinal nationwide retrospective study, 8 years (2014-2021) of sputum samples from presumptively drug-resistant tuberculosis patients from all regions of Gabon were referred to the national tuberculosis reference laboratory. Samples were analysed using GeneXpert MTB/RIF and Genotype MTBDRsl version 2/Line Probe Assay.
RESULTS: Of 3057 sputum samples from presumptive tuberculosis patients, both from local hospital and from referral patients, 334 were RR-TB. The median patient age was 33 years (interquartile range 26-43); one third was newly diagnosed drug-resistant tuberculosis patients; one-third was HIV-positive. The proportion of men with RR-TB was significantly higher than that of women (55% vs 45%; $p < 0.0001$). Patients aged 25-35 years were most affected (32%; 108/334). The cumulative incidence of RR-TB was 17 (95% CI 15-19)/100,000 population over 8 years. The highest incidences were observed in 2020 and 2021. A total of 281 samples were analysed for second-line drug resistance. The proportions of study participants with MDR-TB, pre-XDR-TB and XDR-TB were 90.7% (255/281), 9% (25/281) and 0.3% (1/281), respectively. The most-common mutations in fluoroquinolones resistance isolates was gyrA double mutation gyrA MUT3B and MUT3C (23%; 4/17). Most (64%; 6/8) second-line injectable drugs resistance isolates were characterised by missing both rrs WT2 and MUT2 banding.
CONCLUSION: The increasing incidence of MDR-TB infection in Gabon is alarming. It is highest in the 25-35 years age category. The incidence of MDR-TB infection in treatment-naïve patients calls for case finding and contact tracing strategy improvement.

DOI: 10.1007/s15010-022-01941-5
PMCID: PMC9616411
PMID: 36307576

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

15. **Evidence for Implementation: Management of TB in HIV and Pregnancy.**

Curr HIV/AIDS Rep. 2022 Oct 29:1-16. doi: 10.1007/s11904-022-00641-x. Online

ahead of print.

Jones AJ(1), Mathad JS(2), Dooley KE(3), Eke AC(4).

PURPOSE OF REVIEW: Pregnant people living with HIV (PLWH) are at especially high risk for progression from latent tuberculosis infection (LTBI) to active tuberculosis (TB) disease. Among pregnant PLWH, concurrent TB increases the risk of complications such as preeclampsia, intrauterine fetal-growth restriction, low birth weight, preterm-delivery, perinatal transmission of HIV, and admission to the neonatal intensive care unit. The grave impact of superimposed TB disease on maternal morbidity and mortality among PLWH necessitates clear guidelines for concomitant therapy and an understanding of the pharmacokinetics (PK) and potential drug-drug interactions (DDIs) between antitubercular (anti-TB) agents and antiretroviral therapy (ART) in pregnancy.
RECENT FINDINGS: This review discusses the currently available evidence on the use of anti-TB agents in pregnant PLWH on ART. Pharmacokinetic and safety studies of anti-TB agents during pregnancy and postpartum are limited, and available data on second-line and newer anti-TB agents used in pregnancy suggest that several research gaps exist. DDIs between ART and anti-TB agents can decrease plasma concentration of ART, with the potential for perinatal transmission of HIV. Current recommendations for the treatment of LTBI, drug-susceptible TB, and multidrug-resistant TB (MDR-TB) are derived from observational studies and case reports in pregnant PLWH. While the use of isoniazid, rifamycins, and ethambutol in pregnancy and their DDIs with various ARTs are well-characterized, there is limited data on the use of pyrazinamide and several new and second-line antitubercular drugs in pregnant PLWH. Further research into treatment outcomes, PK, and safety data for anti-TB agent use during pregnancy and postpartum is urgently needed.

DOI: 10.1007/s11904-022-00641-x
PMCID: PMC9617238
PMID: 36308580

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

16. **Resistance and tolerance of Mycobacterium tuberculosis to antimicrobial agents-How M. tuberculosis can escape antibiotics.**

WIREs Mech Dis. 2022 Nov;14(6):e1573. doi: 10.1002/wsbm.1573. Epub 2022 Jun 26.

Li H(1), Yuan J(1), Duan S(2), Pang Y(1).

Tuberculosis (TB) poses a serious threat to public health worldwide since it was discovered. Until now, TB has been one of the top 10 causes of death from a single infectious disease globally. The treatment of active TB cases majorly relies on various anti-tuberculosis drugs. However, under the selection pressure by drugs, the continuous evolution of Mycobacterium tuberculosis (Mtb) facilitates the emergence of drug-resistant strains, further resulting in the accumulation of tubercle bacilli with multiple drug resistance, especially deadly multidrug-resistant TB and extensively drug-resistant TB. Researches on the mechanism of drug action and drug resistance of Mtb provide a new scheme for clinical management of TB patients, and prevention of drug resistance. In this review, we summarized the molecular mechanisms of drug resistance of existing anti-TB drugs to better understand the evolution of drug resistance of Mtb, which will provide more effective strategies against drug-resistant TB, and accelerate the achievement of the EndTB Strategy by 2035. This article is categorized under: Infectious Diseases > Molecular and Cellular Physiology.

DOI: 10.1002/wsbm.1573
PMID: 35753313 [Indexed for MEDLINE]

17. **Quantification of multidrug-resistant M. tuberculosis bacilli in sputum during the first 8 weeks of treatment.**

Int J Tuberc Lung Dis. 2022 Nov 1;26(11):1058-1064. doi: 10.5588/ijtld.21.0741.

Smith-Jeffcoat SE(1), Eisenach KD(2), Joloba M(3), Ssengooba W(3), Namaganda C(3), Nsereko M(4), Okware B(4), Cavanaugh JS(1), Cegielski JP(1).

SETTING: Mulago Hospital, Kampala, Uganda.OBJECTIVE: To quantify Mycobacterium tuberculosis in sputum during the first 8 weeks of pulmonary multidrug-resistant TB (MDR-TB) treatment.DESIGN: We enrolled consecutive adults with pulmonary MDR-TB treated according to national guidelines. We collected overnight sputum samples before treatment and weekly. Sputum samples were cultured on Middlebrook 7H11S agar to measure colony-forming units per mL (cfu/mL) and in MGIT™ 960™ media to measure time to detection (TTD). Linear mixed-effects regression was used to estimate the relational change in log₁₀ cfu/mL and TTD.RESULTS: Twelve adults (median age: 27 years) were enrolled. Half were women, and two-thirds were HIV-positive. At baseline, median log₁₀ cfu/mL was 5.1, decreasing by 0.29 log₁₀ cfu/mL/week. The median TTD was 116.5 h, increasing in TTD by

36.97 h/week. The weekly change was greater in the first 2 weeks (-1.04 log₁₀ cfu/mL/week and 120.02 h/week) than in the remaining 6 weeks (-0.17 log₁₀ cfu/mL/week and 26.11 h/week).CONCLUSION: Serial quantitative culture measures indicate a slow, uneven rate of decline in sputum M. tuberculosis over 8 weeks of standardized pulmonary MDR-TB treatment.

DOI: 10.5588/ijtld.21.0741
PMID: 36281051 [Indexed for MEDLINE]

18. **Tuberculosis in Children Living With HIV: Ongoing Progress and Challenges.**

J Pediatric Infect Dis Soc. 2022 Oct 31;11(Supplement_3):S72-S78. doi: 10.1093/jpids/piac060.

Vonasek BJ(1), Rabie H(2)(3), Hesseling AC(4), Garcia-Prats AJ(1)(4).

There has been much recent progress on control of the tuberculosis (TB) and human immunodeficiency virus (HIV) epidemics globally. However, advances in children have lagged behind, and TB-HIV coinfection continues to be a major driver of pediatric mortality in many settings. This review highlights recent research findings in the areas of prevention, diagnosis, and treatment of HIV-associated childhood TB. Key areas for future research are defined. Current prevention efforts such as vaccination, TB symptom screening, and TB preventive treatment are demonstrated as beneficial but need to be optimized for children living with HIV (CLHIV). Diagnosis of HIV-associated TB in children remains a major challenge, depending heavily on clinicians' ability to judge an array of signs, symptoms, and imaging findings, but there are a growing number of promising diagnostic tools with improved accuracy and feasibility. Treatment of TB-HIV coinfection has also seen recent progress with more evidence demonstrating the safety and effectiveness of shorter regimens for treatment of TB infection and disease and improved understanding of interactions between antiretrovirals and TB medications. However, several evidence gaps on drug-drug interactions persist, especially for young children and those with drug-resistant TB. Accelerated efforts are needed in these areas to build upon current progress and reduce the burden of TB on CLHIV.

DOI: 10.1093/jpids/piac060
PMID: 36314545 [Indexed for MEDLINE]

19. **Rapid Identification of Drug Resistance and Phylogeny in M. tuberculosis, Directly from Sputum Samples.**

Microbiol Spectr. 2022 Oct 26;10(5):e0125222. doi: 10.1128/spectrum.01252-22. Epub 2022 Sep 14.

Barbosa-Amezcua M(1), Cuevas-Córdoba B(1)(2), Fresno C(3)(4), Haase-Hernández JI(3), Carrillo-Sánchez K(5), Mata-Rocha M(6), Muñoz-Torrico M(7), Bäcker C(8), González-Covarrubias V(1), Alaez-Verson C(5), Soberón X(1)(9).

Tuberculosis (TB) remains one of the most important infectious diseases globally. Establishing a resistance profile from the initial TB diagnosis is a priority. Rapid molecular tests evaluate only the most common genetic variants responsible for resistance to certain drugs, and Whole Genome Sequencing (WGS) needs culture prior to next-generation sequencing (NGS), limiting their clinical value. Targeted sequencing (TS) from clinical samples avoids these drawbacks, providing a signature of genetic markers that can be associated with drug resistance and phylogeny. In this study, a proof-of-concept protocol was developed for detecting genomic variants associated with drug resistance and for the phylogenetic classification of Mycobacterium Tuberculosis (Mtb) in sputum samples. Initially, a set of Mtb reference strains from the WHO were sequenced (WGS and TS). The results from the protocol agreed >95% with WHO reported data and phenotypic drug susceptibility testing (pDST). Lineage genetics results were 100% concordant with those derived from WGS. After that, the TS protocol was applied to sputum samples from TB patients to detect resistance to first- and second-line drugs and derive phylogeny. The accuracy was >90% for all evaluated drugs, except Eto/Pto (77.8%), and 100% were phylogenetically classified. The results indicate that the described protocol, which affords the complete drug resistance profile and phylogeny of Mtb from sputum, could be useful in the clinical area, advancing toward more personalized and more effective treatments in the near future. IMPORTANCE The COVID-19 pandemic negatively affected the progress in accessing essential Tuberculosis (TB) services and reducing the burden of TB disease, resulting in a decreased detection of new cases and increased deaths. Generating molecular diagnostic tests with faster results without losing reliability is considered a priority. Specifically, developing an antimicrobial resistance profile from the initial stages of TB diagnosis is essential to ensure appropriate treatment. Currently available rapid molecular tests evaluate only the most common genetic variants responsible for resistance to certain drugs, limiting their clinical value. In this work, targeted sequencing on sputum samples from TB patients was used to identify Mycobacterium tuberculosis mutations in genes associated with drug resistance and to derive a phylogeny of the infecting strain. This protocol constitutes a proof-of-concept toward the goal of helping clinicians select a timely and appropriate treatment

by providing them with actionable information beyond current molecular approaches.

DOI: 10.1128/spectrum.01252-22
PMCID: PMC9602270
PMID: 36102651 [Indexed for MEDLINE]

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

20. **Discovery of new riminophenazine analogues as antimycobacterial agents against drug-resistant Mycobacterium tuberculosis.**

Bioorg Chem. 2022 Nov;128:105929. doi: 10.1016/j.bioorg.2022.105929. Epub 2022 Jun 7.

Zhao X(1), Mei Y(1), Guo Z(1), Si S(1), Ma X(1), Li Y(2), Li Y(3), Song D(1).

Twenty-three new riminophenazine and pyrido[3,2-b]quinoxaline derivatives were prepared and examined for their antimycobacterial activities against Mycobacterium marinum and Mycobacterium tuberculosis H37Rv, taking clofazimine (1) as the lead. Structure-activity relationship (SAR) analysis revealed that the introduction of a heterocycle or diethylamine substituted benzene moiety on the N-5 atom might be beneficial for activity. The most potent compound 7m also displayed enhanced activity against wild-type as well as multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB clinical isolates, with the MICs ranging from 0.08 to 1.25 μg/mL, especially effective toward strain M20A507, resistant to 1. Further mechanism study indicated that its anti-TB activity was independent of cell membrane disruption, but related to NDH-2 reduction and the resulting high ROS production. Our study provides instructive guidance for the further development of clofazimine derivatives into promising antimicrobial agents against MDR and XDR TB.

DOI: 10.1016/j.bioorg.2022.105929
PMID: 35701239 [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.

21. **Whole-genome sequencing of presumptive MDR-TB isolates from a tertiary healthcare setting in Mumbai.**

J Glob Antimicrob Resist. 2022 Oct 20;31:256-262. doi: 10.1016/j.jgar.2022.10.004. Online ahead of print.

Zade A(1), Shah S(1), Hirani N(2), Kondabagil K(3), Joshi A(2), Chatterjee A(4).

OBJECTIVES: Whole-genome sequencing (WGS) of Mycobacterium tuberculosis (MTB), proven to be a better alternative when compared with the combined sensitivity and specificity of all other modalities for diagnosis of tuberculosis (TB), aids epidemiological surveillance investigations by combining the current research with diagnostics. This study was conducted to identify and resolve operational challenges in performing WGS-based drug resistance testing (DRT) for MTB in a TB culture and drug susceptibility testing (DST) laboratory. Three critical, non-redundant steps for WGS-based DRT were tested: viz. DNA extraction, high-throughput paired-end next-generation sequencing (NGS), and genomic analysis pipeline for automated reporting of WGS-based DRT.
METHODS: DNA was extracted from 100 liquid culture isolates on a mycobacterial growth indicator tube (MGIT) using DNEASY Ultraclean Microbial Kit (Qiagen, USA) as per the manufacturer's instructions. Illumina paired-end sequencing was performed. All analysis steps were automated using custom python scripts, requiring no intervention. Variant calling was performed as per the World Health Organization (WHO) technical guide.
RESULTS: The number of cultures resistant to rifampicin, isoniazid, pyrazinamide, ethambutol, and streptomycin was 89, 88, 35, 67, and 73, respectively. Resistance to amikacin, kanamycin, and capreomycin was found in 15, 17, and 15 cultures, respectively. Seventy cultures were resistant to fluoroquinolones, four were resistant to ethionamide, and 12 were resistant to linezolid. Six cultures were resistant to only one of the 18 drugs tested. Seventy-five cultures were resistant to more than three anti-TB drugs. One culture was resistant to 13 of the 18 anti-TB drugs tested for this study. The maximum number of variants were observed in the rpoB gene (n = 93, 93%), wherein the Ser450Leu was the predominant mutation (n = 68, 73%). Ser315Thr was the most common variant (n = 86, 97%) that encoded resistance to isoniazid. The Lys43Arg variant encodes resistance to streptomycin and was the third most predominant variant (n = 65, 89%). In addition to the high levels of resistance observed in the dataset, we also observed a high proportion of Beijing strains (n = 63, 63%).
CONCLUSION: Compared with results from routine diagnostics based on the 'Guidelines on Programmatic Management of Drug-Resistant TB (PMDT) in India', none of the samples had DST available for all 18 drugs. This represents a gap in PMDT guidelines. The WGS-DRT must be considered as the primary DST method after a sample is flagged rifampicin-resistant by cartridge-based nucleic acid

amplification testing (CBNAAT). With several research studies currently underway globally to identify novel variants associated with drug resistance and classifiy their minimum inhibitory coefficients, WGS-DRT presents a scalable technology that updates analytical pipelines, relegating the need for changing microbiological protocols.

DOI: 10.1016/j.jgar.2022.10.004
PMID: 36272707

22. **A revolution in the management of multidrug-resistant tuberculosis.**

Lancet. 2022 Nov 7:S0140-6736(22)02161-4. doi: 10.1016/S0140-6736(22)02161-4. Online ahead of print.

Dheda K(1), Lange C(2).

Erratum in
Lancet. 2022 Nov 18;:

DOI: 10.1016/S0140-6736(22)02161-4
PMID: 36368335

23. **Risk factors for multidrug resistance in tuberculosis patients with diabetes mellitus.**

BMC Infect Dis. 2022 Nov 11;22(1):835. doi: 10.1186/s12879-022-07831-3.

Li S(1), Liang Y(1), Hu X(2).

OBJECTIVE: To study the risk factors and prediction models of multidrug resistance in patients with tuberculosis and diabetes and those with a history of tuberculosis treatment.
METHODS: A total of 256 tuberculosis patients with diabetes who were registered in Luoyang city, Henan Province, from January 2018 to December 2021. Logistic regression analysis was performed to analyse the risk factors for multidrug resistance. ROC curves were used to analyse the predictive model for multidrug resistance.
RESULTS: Age < 65 years old, HbA1c, and a history of tuberculosis treatment were independent risk factors for multidrug resistance in patients with tuberculosis and diabetes ($P < 0.05$). The area under the ROC curve of predictive model for

MDR was 0.878 (95% CI (0.824, 0.932)). Age < 65 years old and HbA1c were independent risk factors for MDR in patients with TB and diabetes with a history of TB treatment. The area under the ROC curve of predictive model for MDR was 0.920 [95% CI (0.831, 0.999)].
CONCLUSION: The predictive model had certain prediction value for the risk of multidrug resistance in patients with tuberculosis and diabetes.

DOI: 10.1186/s12879-022-07831-3
PMCID: PMC9650799
PMID: 36369020 [Indexed for MEDLINE]

Conflict of interest statement: There is no any conflict of interest among the all authors.

24. **High mortality among patients hospitalized for drug-resistant tuberculosis with acquired second-line drug resistance and high HIV prevalence.**

HIV Med. 2022 Nov;23(10):1085-1097. doi: 10.1111/hiv.13318. Epub 2022 May 24.

Anderson K(1)(2), Pietersen E(1), Shepherd BE(3), Bian A(3), Dheda K(1)(4)(5), Warren R(6), Sterling TR(7)(8), van der Heijden YF(7)(8)(9).

OBJECTIVES: We compared mortality between HIV-positive and HIV-negative South African adults with drug-resistant tuberculosis (DR-TB) and high incidence of acquired second-line drug resistance.
METHODS: We performed a retrospective review of DR-TB patients with serial second-line TB drug susceptibility tests (2008-2015) who were hospitalized at a specialized TB hospital. We used Kaplan-Meier analysis and Cox models to examine associations with mortality.
RESULTS: Of 245 patients, the median age was 33 years, 54% were male and 40% were HIV-positive, 96% of whom had ever received antiretroviral therapy (ART). At initial drug resistance detection, 99% of patients had resistance to at least rifampicin and isoniazid, and 18% had second-line drug resistance (fluoroquinolones and/or injectable drugs). At later testing, 88% of patients had acquired additional second-line drug resistance. Patient-initiated treatment interruptions (> 2 months) occurred in 47%. Mortality was 79%. Those with HIV had a shorter time to death (p = 0.02; log-rank): median survival time from DR-TB treatment initiation was 2.44 years [95% confidence interval (CI): 2.09-3.15] versus 3.99 years (95% CI: 3.12-4.75) for HIV-negative patients. HIV-positive patients who received ART within 6 months before DR-TB treatment had a higher mortality hazard than HIV-negative patients [adjusted hazard ratio

(aHR) ratio = 1.82, 95% CI: 1.21-2.74]. By contrast, HIV-positive patients who did not receive ART within 6 months before DR-TB treatment did not have a significantly higher mortality hazard than HIV-negative patients (aHR = 1.09; 95% CI: 0.72-1.65), although those on ART had lower median CD4 counts than those not on ART (157 vs. 281 cells/μL, respectively; p = 0.02).
CONCLUSIONS: A very high incidence of acquired second-line drug resistance and high overall mortality were observed, reinforcing the need to reduce the risk of acquired resistance and for more effective treatment.

DOI: 10.1111/hiv.13318
PMCID: PMC9588462
PMID: 35608016 [Indexed for MEDLINE]

Conflict of interest statement: Conflict of interest: KA received funding from Viiv Healthcare which is not related to this project. All other authors: no conflict of interest declared.

25. **Effectiveness and Safety of Bedaquiline-based, Modified All-oral 9-11-month Treatment Regimen for Rifampicin-Resistant Tuberculosis in Vietnam.**

Int J Infect Dis. 2022 Nov 10:S1201-9712(22)00592-6. doi: 10.1016/j.ijid.2022.11.007. Online ahead of print.

Mai Phuong NT(1), Hai Minh LT(1), Collette Merle CS(2), Pedrazzoli D(3), Linh NN(3), Decroo T(4), Hoa NB(1), Thuy HTT(1), Nhung NV(5).

BACKGROUND: WHO recommends a 7-drug 9-11-month rifampicin-resistant tuberculosis (RR-TB) short treatment regimen (STR). To reduce the pill burden, we assessed the safety and effectiveness of a 5-drug 9-11-month modified STR (mSTR).
METHODS: Prospective cohort study of an all-oral mSTR (comprising bedaquiline, levofloxacin, linezolid, clofazimine and/or pyrazinamide) for RR-TB patients without confirmed fluoroquinolone resistance, enrolled in Vietnam between 2020-2021.
RESULTS: One hundred eight patients were enrolled. Sixty-three of 74 (85%) achieved culture conversion at 2 months. Of 106 evaluated, 95 (90%) were successfully treated, 6 (6%) were lost-to-follow-up, 1 (1%) died and 4 (4%) had treatment failure, including 3 with permanent regimen change due to adverse events (AE) and 1 with culture reversion. Thirty-two (30% of 108) patients encountered at least one AE. Of 45 AEs recorded, 13 (29%) were serious (hospitalization, life threatening or death). The median time to AE was 3 months

(IQR:2-5). Twenty-six AEs led to regimen adaptation: either dose reduction (N=1), drug temporary interruption (N=19), or drug permanent discontinuation (N=6, 4 attributed to linezolid).
CONCLUSION: The high treatment success 5-drug mSTR may replace the 7-drug regimen in routine care. AEs were frequent, but manageable in most patients. Active AEs monitoring is essential, particularly when using linezolid throughout.

DOI: 10.1016/j.ijid.2022.11.007
PMID: 36372364

26. **Identification of Arginine Phosphorylation in Mycolicibacterium smegmatis.**

Microbiol Spectr. 2022 Oct 26;10(5):e0204222. doi: 10.1128/spectrum.02042-22. Epub 2022 Oct 10.

Ogbonna EC(1), Anderson HR(2), Schmitz KR(1)(2).

Tuberculosis is a leading cause of worldwide infectious mortality. The prevalence of multidrug-resistant Mycobacterium tuberculosis infections drives an urgent need to exploit new drug targets. One such target is the ATP-dependent protease ClpC1P1P2, which is strictly essential for viability. However, few proteolytic substrates of mycobacterial ClpC1P1P2 have been identified to date. Recent studies in Bacillus subtilis have shown that the orthologous ClpCP protease recognizes proteolytic substrates bearing posttranslational arginine phosphorylation. While several lines of evidence suggest that ClpC1P1P2 is similarly capable of recognizing phosphoarginine-bearing proteins, the existence of phosphoarginine modifications in mycobacteria has remained in question. Here, we confirm the presence of posttranslational phosphoarginine modifications in Mycolicibacterium smegmatis, a nonpathogenic surrogate of M. tuberculosis. Using a phosphopeptide enrichment workflow coupled with shotgun phosphoproteomics, we identified arginine phosphosites on several functionally diverse targets within the M. smegmatis proteome. Interestingly, phosphoarginine modifications are not upregulated by heat stress, suggesting divergent roles in mycobacteria and Bacillus. Our findings provide new evidence supporting the existence of phosphoarginine-mediated proteolysis by ClpC1P1P2 in mycobacteria and other actinobacterial species. IMPORTANCE Mycobacteria that cause tuberculosis infections employ proteolytic pathways that modulate cellular behavior by destroying specific proteins in a highly regulated manner. Some proteolytic enzymes have emerged as novel antibacterial targets against drug-resistant tuberculosis infections. However, we have only a limited understanding of how

these enzymes function in the cell and how they select proteins for destruction. Some proteolytic enzymes are capable of recognizing proteins that carry an unusual chemical modification, arginine phosphorylation. Here, we confirm the existence of arginine phosphorylation in mycobacterial proteins. Our work expands our understanding of a promising drug target in an important global pathogen.

DOI: 10.1128/spectrum.02042-22
PMCID: PMC9604228
PMID: 36214676 [Indexed for MEDLINE]

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

27. **Diagnostic Capacities for Multidrug-Resistant Tuberculosis in the World Health Organization European Region: Action is Needed by all Member States.**

J Mol Diagn. 2022 Nov;24(11):1189-1194. doi: 10.1016/j.jmoldx.2022.07.005. Epub 2022 Aug 11.

Maurer FP(1), Shubladze N(2), Kalmambetova G(3), Felker I(4), Kuchukhidze G(5), Köser CU(6), Cirillo DM(7), Drobniewski F(8), Yedilbayev A(5), Ehsani S(9); European Laboratory Initiative on TB, HIV and Viral Hepatitis.

Collaborators: Avellón A, Chulanov V, Cirillo DM, Drobniewski F, Felker I, Kalmambetova G, Köser CU, Maurer FP, Niemann S, Noroc E, Paredes R, Shubladze N, Simões D, Skrahina A, Stanojevic M.

The World Health Organization (WHO) recently revised its guidelines for rapid diagnosis of drug-resistant tuberculosis (TB). This study aimed to investigate if TB reference diagnostic services are prepared to support these revisions. An online survey was performed among 44 TB National Reference Laboratories (NRLs) in the WHO European Region. Questions addressed the use of WHO-recommended molecular techniques for the diagnosis of drug-resistant TB, the techniques applied to investigate antimicrobial resistance, and questions on quality assurance. Among 35 of 44 (80%) participating NRLs, 29 of 35 (83%) reported using the GeneXpert platform as the initial test to detect Mycobacterium tuberculosis complex and rifampicin resistance. Five laboratories reported using another WHO-recommended, moderate-complexity, automated nucleic acid amplification test for detection of Mycobacterium tuberculosis complex and resistance to rifampicin and isoniazid. Most (32 of 35; 91%) NRLs reported the capacity to test second-line drugs that have been in clinical use for many years (fluoroquinolones, linezolid, and injectable agents). Only 23 of 35 (66%) and 21 of 35 (60%) NRLs reported the capacity to test bedaquiline and clofazimine.

Further efforts will be needed to improve the availability of quality-controlled testing against WHO Group A and Group B drugs. Earlier considerations on the scale-up of diagnostic capacities should be enforced as part of future approval processes for new antimycobacterial agents.

DOI: 10.1016/j.jmoldx.2022.07.005
PMID: 35964846 [Indexed for MEDLINE]

28. **Regional distribution of Mycobacterium tuberculosis infection and resistance to rifampicin and isoniazid as determined by high-resolution melt analysis.**

BMC Infect Dis. 2022 Oct 31;22(1):812. doi: 10.1186/s12879-022-07792-7.

Wang Z(1)(2), Guo T(1), Jiang T(1), Zhao Z(3), Zu X(2), Li L(1), Zhang Q(1), Hou Y(4), Song K(2), Xue Y(5).

BACKGROUND: Identifying the transmission mode and resistance mechanism of Mycobacterium tuberculosis (MTB) is key to prevent disease transmission. However, there is a lack of regional data. Therefore, the aim of this study was to identify risk factors associated with the transmission of MTB and regional patterns of resistance to isoniazid (INH) and rifampicin (RFP), as well as the prevalence of multidrug-resistant tuberculosis (MDR-TB).
METHODS: High-resolution melt (HRM) analysis was conducted using sputum, alveolar lavage fluid, and pleural fluid samples collected from 17,515 patients with suspected or confirmed MTB infection in the downtown area and nine counties of Luoyang City from 2019 to 2021.
RESULTS: Of the 17,515 patients, 82.6% resided in rural areas, and 96.0% appeared for an initial screening. The HRM positivity rate was 16.8%, with a higher rate in males than females (18.0% vs. 14.1%, $p < 0.001$). As expected, a positive sputum smear was correlated with a positive result for HRM analysis. By age, the highest rates of MTB infection occurred in males (22.9%) aged 26-30 years and females (28.1%) aged 21-25. The rates of resistance to RFP and INH and the incidence of MDR were higher in males than females (20.5% vs. 16.1%, $p < 0.001$, 15.9% vs. 12.0%, $p < 0.001$ and 12.9% vs. 10.2%, $p < 0.001$, respectively). The HRM positivity rate was much higher in previously treated patients than those newly diagnosed for MTB infection. Notably, males at the initial screening had significantly higher rates of HRM positive, INH resistance, RFP resistance, and MDR-TB than females (all, $p < 0.05$), but not those previously treated for MTB infection. The HRM positivity and drug resistance rates were much higher in the urban vs. rural population. By

multivariate analyses, previous treatment, age < 51 years, residing in an urban area, and male sex were significantly and positively associated with drug resistance after adjusting for smear results and year of testing.
CONCLUSION: Males were at higher risks for MTB infection and drug resistance, while a younger age was associated with MTB infection, resistance to INH and RFP, and MDR-TB. Further comprehensive monitoring of resistance patterns is needed to control the spread of MTB infection and manage drug resistance locally.

DOI: 10.1186/s12879-022-07792-7
PMCID: PMC9620668
PMID: 36316637 [Indexed for MEDLINE]

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

29. **Outcomes of patients undergoing lung resection for drug-resistant TB and the prognostic significance of pre-operative positron emission tomography/computed tomography (PET/CT) in predicting treatment failure.**

EClinicalMedicine. 2022 Nov 3;55:101728. doi: 10.1016/j.eclinm.2022.101728. eCollection 2023 Jan.

Calligaro GL(1), Singh N(1), Pennel TC(2), Steyn R(3), Brink A(3), Esmail A(1), Mottay L(1), Oelofse S(1), Mastrapa BL(4), Basera W(5)(6), Manning K(5), Ofoegbu C(2), Linegar A(2), Dheda K(1)(7).

BACKGROUND: Surgery remains an adjunctive treatment for drug-resistant tuberculosis (DR-TB) treatment failure despite the use of bedaquiline. However, there are few data about the role of surgery when combined with newer drugs. There are no outcome data from TB endemic countries, and the prognostic significance of pre-operative PET-CT remains unknown.
METHODS: We performed a prospective observational study of 57 DR-TB patients referred for surgery at Groote Schuur Hospital between 2010 and 2016. PET-CT was performed if there was nodal disease or disease outside the area of planned resection but did not influence treatment decisions. 24-month treatment success post-surgery (cure or treatment completion), including all-cause mortality, was determined.
FINDINGS: 35/57 (61.4%) patients (median age 40 years; 26% HIV-infected) underwent surgery and 22/57 (38.6%) did not (11 patients were deemed unsuitable due to bilateral cavitary disease and 11 patients declined surgery). Treatment

failure was significantly lower in those who underwent surgery compared to those eligible but declined surgery [15/35 (43%) versus 11/11 (100%); relative risk 0.57 (0.42-0.76); p < 0.01). In patients treated with surgery, a post-operative regimen containing bedaquiline was associated with a lower odds of treatment failure [OR (95%CI) 0.06 (0.00-0.48); p = 0.007]. Pre-operative PET-CT (n = 25) did not predict treatment outcome.
INTERPRETATION: Resectional surgery for DR-TB combined with chemotherapy was associated with significantly better outcomes than chemotherapy alone. A post-operative bedaquiline-containing regimen was associated with improved outcome; however, this finding may have been confounded by higher use of bedaquiline and less loss to follow-up in the surgical group. However, PET-CT had no prognostic value. These data inform clinical practice in TB-endemic settings.
FUNDING: This work was supported by the South African MRC (RFA-EMU-02-2017) and the EDCTP (TMA-2015SF-1043 & TMA- 1051-TESAII).

DOI: 10.1016/j.eclinm.2022.101728
PMCID: PMC9646880
PMID: 36386040

Conflict of interest statement: There are no conflicts of interest to declare for any authors.

30. **Efficacy and tolerability of concomitant use of bedaquiline and delamanid for multidrug- and extensively drug-resistant tuberculosis: a systematic review and meta-analysis.**

Clin Infect Dis. 2022 Nov 4:ciac876. doi: 10.1093/cid/ciac876. Online ahead of print.

Holmgaard FB(1)(2), Guglielmetti L(3)(4), Lillebaek T(5)(6), Andersen ÅB(7), Wejse C(1)(2), Dahl VN(1)(2)(5).

The introduction of two novel drugs, bedaquiline and delamanid, has given hope for better and shorter treatments of drug-resistant tuberculosis. A systematic review was conducted to evaluate the efficacy and safety of concomitant bedaquiline and delamanid administration. Pooled estimates of WHO-defined favorable treatment outcome and significant QTc-interval prolongation (QTc ≥500 ms or ≥60 ms increase from baseline) were calculated using a random effects model. Thirteen studies including a total of 1031 individuals with multidrug-resistant/rifampicin-resistant tuberculosis who received bedaquiline

and delamanid were included. The pooled estimate of favorable treatment outcome was 73.1% (95%CI: 64.3-81.8). Sputum culture conversion at six months ranged from 61-95%. Overall, the pooled proportion of QTc-prolongation was 7.8% (95%CI: 4.1-11.6) and few cardiac events were reported (0.8%, n = 6/798). Rates of sputum culture conversion and favorable treatment outcome were high in patients treated concomitantly with bedaquiline and delamanid, and the treatment seemed tolerable with low rates of clinically significant cardiac toxicity.

DOI: 10.1093/cid/ciac876
PMID: 36331978

31. **Survival Trend of Tuberculosis Patients and Risk Factors Associated with Mortality and Developing Drug-Resistant Tuberculosis in Hospital Pulau Pinang, Malaysia: A Retrospective Study.**

Adv Respir Med. 2022 Nov 14;90(6):467-482. doi: 10.3390/arm90060054.

Yaghi AR(1), Shaheed HS(2), Harun SN(1), Hyder Ali IA(3), Khan AH(1).

BACKGROUND: Multidrug resistance TB (MDR-TB) has emerged as a public health issue worldwide, and the mortality rate is worrying. Therefore, this study was conducted to investigate the factors related to MDR-TB occurrence and the survival experience of TB patients.
METHODS: A retrospective cohort study was conducted at Hospital Pulau Pinang in Malaysia. Medical records of active TB patients from 2014-2018 were reviewed. Cox regression was used to identify the factors associated with MDR-TB development and mortality among TB patients.
RESULTS: The patients had a mean age of 48.84 ± 16.713 years, and a majority of the Chinese race (46.4%). Out of 351 TB patients, 325 (92.6%) were drug-susceptible TB, and 26 (7.4%) were diagnosed with MDR-TB. Among drug-susceptible TB patients, 245 (75.4%) achieved successful outcomes, and 73 (22.5%) passed away. In multivariable Cox regression, drug addiction, levels of white blood cells, urea, platelets, and albumin were significantly associated with death. Relapsed TB, alcohol consumption, and being single were significant risk factors for MDR-TB development.
CONCLUSION: Patients achieved a success rate of 75.4%, which is encouraging but still far below the WHO target (at least an 85% success rate) and has room for further improvement.

DOI: 10.3390/arm90060054
PMID: 36412638 [Indexed for MEDLINE]

32. **Primary Multidrug-resistant Tuberculosis in a Surgeon Secondary to a Needlestick Injury: A Neglected Problem.**

Infect Drug Resist. 2022 Nov 14;15:6651-6657. doi: 10.2147/IDR.S387363. eCollection 2022.

Yang M(#)(1)(2), Xu M(#)(3), Zhang X(1)(2), Zhao H(1)(2), Hu J(1)(2), Wang J(1)(2).

Healthcare workers (HCWs) are highly at risk for tuberculosis (TB) exposure, particularly those in high TB burden countries. Inoculation TB secondary to needlestick injury is uncommon but can occur in HCWs. Herein, we report an unusual case of primary multidrug-resistant tuberculosis (MDR-TB) in a surgeon secondary to a needlestick injury while performing thoracentesis on a TB patient, and the surgeon recovered and returned to work after 22 months of anti-TB treatment. We searched the PubMed database and identified 19 cases of inoculation TB secondary to sharp injury in HCWs including the present case. Those cases highlight that primary inoculation of TB even MDR-TB infection should not be neglected in patients suffered needlestick injury when the sharp instrument suspected or confirmed contaminated with TB. In this situation, if the HCWs need for additional protection or prophylactic anti-TB is worthy of further study.

DOI: 10.2147/IDR.S387363
PMCID: PMC9673929
PMID: 36406864

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

33. **A battery of tandem mass spectrometry assays with stable isotope-dilution for the quantification of 15 anti-tuberculosis drugs and two metabolites in patients with susceptible-, multidrug-resistant- and extensively drug-resistant tuberculosis.**

J Chromatogr B Analyt Technol Biomed Life Sci. 2022 Nov 15;1211:123456. doi: 10.1016/j.jchromb.2022.123456. Epub 2022 Sep 20.

Mercier T(1), Desfontaine V(1), Cruchon S(1), Da Silva Pereira Clara JA(1), Briki M(1), Mazza-Stalder J(2), Kajkus A(1), Burger R(3), Suttels V(4), Buclin T(5), Opota O(6), Koehler N(7), Sanchez Carballo PM(7), Lange C(8), André P(5), Decosterd LA(1), Choong E(9).

OBJECTIVE: Anti-tuberculosis (antiTB) drugs are characterized by an important inter-interindividual pharmacokinetic variability poorly predictable from individual patients' characteristics. Therapeutic drug monitoring (TDM) may therefore be beneficial for patients with Mycobacterium tuberculosis infection, especially for the management of multidrug/extensively drug resistant-(MDR/XDR)-TB. Our objective was to develop robust HPLC-MS/MS methods for plasma quantification of 15 antiTB drugs and 2 metabolites, namely rifampicin, isoniazid plus N-acetyl-isoniazid, pyrazinamide, ethambutol (the conventional quadritherapy for susceptible TB) as well as combination of agents against MDR/XDR-TB: bedaquiline, clofazimine, delamanid and its metabolite M1, levofloxacin, linezolid, moxifloxacin, pretomanid, rifabutin, rifapentine, sutezolid, and cycloserine.
METHODS: Plasma protein precipitation was used for all analytes except cycloserine, which was analyzed separately after derivatization with benzoyl chloride. AntiTB quadritherapy drugs (Pool1) were separated by Hydrophilic Interaction Liquid Chromatography (column Xbridge BEH Amide, 2.1 × 150 mm, 2.5 µm, Waters®) while MDR/XDR-TB agents (Pool 2) and cycloserine (as benzoyl derivative) were analyzed by reverse phase chromatography on a column XSelect HSS T3, 2.1 × 75 mm, 3.5 µm (Waters®). All runs last <7 min. Quantification was performed by selected reaction monitoring electrospray tandem mass spectrometry, using stable isotopically labelled internal standards.
RESULTS: The method covers the clinically relevant plasma levels and was extensively validated based on FDA recommendations, with intra- and inter-assay precision (CV) < 15% over the validated ranges. Application of the method is illustrated by examples of TDM for two patients treated for drug-susceptible- and MDR-TB.
CONCLUSION: Such convenient extraction methods and the use of stable isotope-labelled drugs as internal standards provide an accurate and precise quantification of plasma concentrations of all major clinically-used antiTB drugs regimens and is optimally suited for clinically efficient TDM against tuberculosis.

DOI: 10.1016/j.jchromb.2022.123456
PMID: 36240540 [Indexed for MEDLINE]

Conflict of interest statement: Declaration of Competing Interest The authors

declare the following financial interests/personal relationships which may be considered as potential competing interests: [Eva Choong reports equipment, drugs, or supplies was provided by Otsuka Pharmaceutical Co Ltd. Laurent Decosterd reports financial support was provided by Swiss National Science Foundation. Christoph Lange reports financial support was provided by German Center for Infection Research Hamburg-Lübeck-Borstel-Riems Site. Laurent Decosterd reports financial support was provided by University of Lausanne.].

34. **Transcriptional Biomarkers for Treatment Monitoring of Pulmonary Drug-Resistant Tuberculosis: Protocol for a Prospective Observational Study in Indonesia.**

Trop Med Infect Dis. 2022 Oct 22;7(11):326. doi: 10.3390/tropicalmed7110326.

Parwati I(1), Pitaloka DAE(2)(3), Chaidir L(3)(4).

Many blood-based gene expression biomarkers for monitoring tuberculosis (TB) treatment have been suggested so far, but promising biomarker results for drug-resistant TB treatment response have not been studied. This protocol presents a prospective observational study in Indonesia to profile the human blood transcriptome for predicting the response to drug-resistant TB treatment, focusing on pulmonary TB, and to adapt the specific RNA signature to the qRT-PCR platform. Longitudinal blood samples will be collected from 44 subjects with rifampicin resistant TB, confirmed by Xpert MTB/RIF, and 52 healthy controls. RNA-Seq will be performed to identify changes in the transcriptome following TB treatment. A discriminative RNA signature will be chosen and translated into a score for use in a quantitative PCR-based assay. This study will provide crucial information to guide the discovery and design of a clinically implementable tool to monitor the response of TB treatment.

DOI: 10.3390/tropicalmed7110326
PMID: 36355869

35. **First insights into the phylogenetic diversity of Mycobacterium tuberculosis in Kuwait and evaluation of REBA MTB-MDR assay for rapid detection of MDR-TB.**

PLoS One. 2022 Oct 20;17(10):e0276487. doi: 10.1371/journal.pone.0276487. eCollection 2022.

Al-Mutairi NM(1), Ahmad S(1), Mokaddas E(1)(2), Al-Hajoj S(3).

Early detection of Mycobacterium tuberculosis (Mtb) in clinical specimens, its susceptibility to anti-TB drugs and disruption of infection transmission to new

hosts are essential components for global tuberculosis (TB) control efforts. This study investigated major Mtb genotypes circulating in Kuwait and evaluated the performance of REBA MTB-MDR (REBA) test in comparison to GenoType MTBDRplus (gMTBDR+) assay for rapid detection of resistance of Mtb to isoniazid and rifampicin (MDR-TB). M. tuberculosis isolates (n = 256) originating predominantly from expatriate patients during a 6-month period were tested by spoligotyping and a dendrogram was created by UPGMA using MIRU-VNTRplus software. Phenotypic drug susceptibility testing (DST) was performed by MGIT 960 system. Genotypic DST for isoniazid and rifampicin was done by REBA and gMTBDR+ assays. Spoligotyping assigned 188 (73.4%) isolates to specific spoligotype international type (SIT) while 68 isolates exhibited orphan patterns. All major M. tuberculosis lineages were detected and EAI, CAS and Beijing families were predominant. Phylogenetic tree showed 131 patterns with 105 isolates exhibiting a unique pattern while 151 isolates clustered in 26 patterns. Fifteen isolates were resistant to one/more drugs. REBA and gMTBDR+ detected isoniazid resistance in 11/12 and 10/12 and rifampicin resistance in 4/5 and 4/5 resistant isolates, respectively. The diversity of SIT patterns are highly suggestive of infection of most expatriate patients with unique Mtb strains, likely acquired in their native countries before their arrival in Kuwait. Both, REBA and gMTBDR+ assays performed similarly for detection of resistance of Mtb to isoniazid and rifampicin for rapid detection of MDR-TB.

DOI: 10.1371/journal.pone.0276487
PMCID: PMC9584360
PMID: 36264939 [Indexed for MEDLINE]

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

36. **Adherence Measured Using Electronic Dose Monitoring is Associated with Emergent Antiretroviral Resistance and Poor Outcomes in People with Human Immunodeficiency Virus/AIDS and Multidrug-Resistant Tuberculosis.**

Clin Infect Dis. 2022 Oct 29;75(9):1489-1496. doi: 10.1093/cid/ciac232.

Bateman M(1), Wolf A(2), Chimukangara B(3)(4), Brust JCM(5), Lessells R(6), Amico R(7), Boodhram R(4), Singh N(8), Orrell C(9), Friedland G(10), Naidoo K(4), Padayatchi N(4), O'Donnell MR(2)(4)(11).

BACKGROUND: Medication adherence is known to challenge treatment of human immunodeficiency virus (HIV)/AIDS and multidrug-resistant tuberculosis (MDR-TB). We hypothesized that adherence using electronic dose monitoring (EDM) would identify an antiretroviral therapy (ART) adherence threshold for emergent ART

resistance and predict treatment outcomes in patients with MDR-TB and HIV on ART and bedaquiline-containing TB regimens.
METHODS: A prospective cohort of adults with MDR-TB and HIV on ART and initiating MDR-TB treatment with bedaquiline were enrolled at a public hospital in KwaZulu-Natal, South Africa (PRAXIS Study). Participants received separate EDM devices that measure adherence to bedaquiline and ART (nevirapine or lopinavir/ritonavir). Adherence was calculated cumulatively over 6 months. Participants were followed through completion of MDR-TB treatment. HIV genome sequencing was performed at baseline and 2 and 6 months on samples with HIV RNA ≥1000 copies/mL.
RESULTS: From November 2016 through February 2018, 198 persons with MDR-TB and HIV were enrolled and followed (median, 17.2 months; interquartile range, 12.2-19.6). Eleven percent had baseline ART resistance mutations, and 7.5% developed emergent ART resistance at 6 months. ART adherence was independently associated with ART resistance and mortality. Modeling identified a significant ($P < .001$), linear association between ART adherence and emergent resistance, suggesting a strong association without a specific threshold.
CONCLUSIONS: Our findings highlight the need for ART resistance testing, especially in patients with MDR-TB and HIV, which is currently not the standard of care in resource-limited settings. Despite short follow-up duration, reduced ART adherence was significantly associated with emergent resistance and increased mortality.
CLINICAL TRIALS REGISTRATION: NCT03162107.

DOI: 10.1093/cid/ciac232
PMCID: PMC9617578
PMID: 35352097 [Indexed for MEDLINE]

Conflict of interest statement: Potential conflicts of interest. M. R. O. reports payment or honoraria from Otsuka and the France Foundation and being a board member for fightcovidafrica.org. Richard J. Lessells reports grants or contracts from the NIH and an International epidemiology Databases to Evaluate AIDS (IeDEA) subaward to the University of KwaZulu-Natal from the Universität Bern outside of the submitted work. C. O. reports salary from the University of Cape Town and the Desmond Tutu Health Foundation, honoraria for consulting on an expert panel for ViiV, honoraria for consulting on an expert panel for Merck Sharp & Dohm Corp., a subsidiary of the Merck & Co., Inc. (MSD), and is a member of Data Safety and Monitoring Board for Standard versus double dose dolutegravir in patients with HIV-associated tuberculosis: a phase 2 non-comparative randomised controlled (RADIANT-TB) trial (DSMB for RADINAT TB) and Data Safety

Monitoring Board for Zidovudine, lamivudine and dolutegravir (AXD) Relative to Tenofovir, lamivudine and dolutegravir (TXD) in Second Line Antiretroviral Therapy (ARTIST) Trial: a randomized control trial (DSMB chair for ARTIST). J. C. M. B. reports grants or contracts from the NIH paid to the Albert Einstein College of Medicine outside the scope of this work. All remaining 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.

37. **Pharmacokinetics and Safety of Bedaquiline in Human Immunodeficiency Virus (HIV)-Positive and Negative Older Children and Adolescents With Rifampicin-Resistant Tuberculosis.**

Clin Infect Dis. 2022 Nov 14;75(10):1772-1780. doi: 10.1093/cid/ciac252.

Hughes JA(1), Solans BP(2), Draper HR(1), Schaaf HS(1), Winckler JL(1), van der Laan L(1), Radtke KK(2), Fourie B(3), Wiesner L(4), Hesseling AC(1), Savic RM(2), Garcia-Prats AJ(1)(5).

BACKGROUND: Pharmacokinetic data for bedaquiline in children are limited. We described the pharmacokinetics and safety of bedaquiline in South African children and adolescents receiving treatment for multidrug/rifampicin-resistant tuberculosis (MDR/RR-TB) in routine care.
METHODS: In this observational cohort study, children aged 6-17 years receiving bedaquiline at recommended doses as part of MDR/RR-TB treatment underwent semi-intensive pharmacokinetic sampling. Bedaquiline and the M2 metabolite plasma concentrations were quantified, and nonlinear mixed-effects modeling performed. Pediatric data were described using a pre-established model of bedaquiline pharmacokinetics in adults. The exposure reference was 187 µg · h/mL, the median weekly area under the curve (AUC) of adults at week 24 of treatment with bedaquiline. Safety was assessed through monthly clinical, blood and electrocardiogram monitoring, and treatment outcomes described.
RESULTS: Fifteen children (3 human immunodeficiency virus [HIV]-positive) with median age 13.3 years (range 6.5-16.3) were included. A bedaquiline pharmacokinetic model was adapted to be allometrically scaled in clearance and volume, centered in the median child population weight. Bedaquiline bioavailability was 57% of that in adults. Overall bedaquiline exposures were below target, and AUC reference attainment was achieved in only 3 (20%) children. Ten children experienced 27 adverse events at least possibly related to bedaquiline; no adverse events led to bedaquiline withdrawal. Two adverse events (arthritis and arthralgia) were considered severe, and 2 children had mild QT interval corrected for heart rate using Fridericia's formula (QT) prolongation.

CONCLUSIONS: The evaluated doses of bedaquiline in children ≥ 6 years of age were safe but achieved slightly lower plasma concentrations compared to adults receiving the recommended dose, possibly due to delayed food intake relative to bedaquiline administration.

DOI: 10.1093/cid/ciac252
PMCID: PMC9662178
PMID: 35377434 [Indexed for MEDLINE]

Conflict of interest statement: Potential conflicts of interest. A. G.-P. reports the institution received funding from Otsuka Pharmaceuticals for pediatric trials of delamanid, another new TB drug, payment completed in 2019, and the institution received funding from Unitaid for studies of the PK, safety of other approved second-line TB drugs in children, payment are ongoing to the institution, both outside of the submitted work. H. S. S. reports writing an educational article on “An update on the management of drug-resistant tuberculosis in children” – a general MDR-TB article for Medical Focus (an educational publication for Africa setting) and was also the guest editor for this issue end of 2021 and received a payment of R4000 for the article and R10000 as guest editor was made to self from Ann Lake Publishers (Medical focus issue sponsored by Johnson&Johnson/Janssen). All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

38. **Exploring the Impact of the COVID-19 Pandemic on Tuberculosis Care and Prevention.**

J Pediatric Infect Dis Soc. 2022 Oct 31;11(Supplement_3):S67-S71. doi: 10.1093/jpids/piac102.

Sahu S(1), Wandwalo E(2), Arinaminpathy N(3).

The COVID-19 pandemic has set back the global tuberculosis (TB) response by several years. In 2020, access to TB prevention and care declined sharply, with TB notifications dropping by 18% compared to 2019. Declines were more pronounced in children, with a 24% drop in 0-14 year-olds and a 28% drop in 0-4 year-olds. As a result, in 2020 the number of deaths due to TB increased to 1.5 million across all ages, reversing a decade-long declining trend. Progress toward the UN

High Level Meeting targets for 2022 is at risk, including the targets related to children for TB and drug-resistant TB treatments, and TB preventive therapy. Nonetheless, ending TB by 2030 as envisaged in the Sustainable Development Goals (SDGs) is still possible, but requires increased investments in accelerated case detection, subclinical TB, preventive therapy and an effective vaccine. Investing in TB could prepare the world better for fighting a future airborne pandemic.

DOI: 10.1093/jpids/piac102
PMID: 36314548 [Indexed for MEDLINE]

39. **Programmatic management of rifampicin-resistant tuberculosis with standard regimen in Cameroon: a retrospective cohort study.**

Int J Infect Dis. 2022 Nov;124:81-88. doi: 10.1016/j.ijid.2022.09.012. Epub 2022 Sep 13.

Jouego CG(1), Gils T(2), Piubello A(3), Mbassa V(4), Kuate A(4), Ngono A(5), Belinga E(6), Etoundi A(7), Tollo A(8), Makondi D(9), André E(10), Masumbe P(11), Lynen L(12), Noeske J(13), Decroo T(14).

OBJECTIVES: To describe treatment outcomes for rifampicin-resistant tuberculosis (Rr-TB) started on standard regimen and the frequency of acquired drug resistance in patients treated using the standard treatment regimen (STR) in Cameroon between 2015-2019.
METHODS: This is a retrospective cohort study. Rr-TB patients were initiated on the STR, including a fluoroquinolone (FQ), a second-line injectable drug (SLI), and companion drugs. In case of resistance to fluoroquinolones (FQr) at baseline, FQ, SLI and ethionamide were replaced by bedaquiline, delamanid, and linezolid in a modified treatment regimen (mTR), FQr-mTR. In case of resistance to SLI (SLIr) at baseline, SLI was replaced by linezolid (LZD), SLIr-mTR. Logistic regression and competing risk regression were used to estimate predictors of early (first eight weeks) mortality and overall mortality, respectively.
RESULTS: Of 709 patients started on a standard regimen, treatment success occurred in 84.7% (587/693), 72.7% (8/11) and 100% (10/10) of patients treated with STR, FQr-mTR and SLIr-mTR as final regimens, respectively. Three (0.6%) patients acquired FQr during treatment. Early mortality occurred in 4.1% (29/709) and was associated with being HIV positive, male sex and being

underweight. Overall mortality was associated with missing drug-susceptibility testing results at baseline, being HIV positive, age>40 and male sex.
CONCLUSION: Programmatic management of Rr-TB, with additional second-line drug resistance treated with mTR, resulted in excellent treatment outcomes.

DOI: 10.1016/j.ijid.2022.09.012
PMID: 36108960 [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.

40. **Global trends, regional differences and age distribution for the incidence of HIV and tuberculosis co-infection from 1990 to 2019: results from the global burden of disease study 2019.**

Infect Dis (Lond). 2022 Nov;54(11):773-783. doi: 10.1080/23744235.2022.2092647. Epub 2022 Jul 7.

Wang Y(1), Jing W(1), Liu J(1), Liu M(1).

BACKGROUND: People living with human immunodeficiency virus (HIV) are more likely to develop tuberculosis (TB), and their co-infection (HIV-TB) increases the risk of death. We aimed to describe the global trends, regional differences and age distribution of HIV-TB.
METHODS: Annual new cases, age-standardized incidence rates (ASRs) and age-specific incidence rates with 95% uncertainty intervals (UIs) of HIV-infected drug-susceptible tuberculosis (HIV-DS-TB), HIV-infected multidrug-resistant tuberculosis without extensive drug resistance (HIV-MDR-TB) and HIV-infected extensively drug-resistant tuberculosis (HIV-XDR-TB) during 1990-2019 were collected from the Global Burden of Disease Study 2019. To reveal the trends of HIV-TB by region and age, the percentage change of new cases and estimated annual percentage change (EAPC) of ASRs were calculated.
RESULTS: The ASR of HIV-XDR-TB increased significantly by an average of 14.77% (95% CI: 11.05%-18.62%) per year during 1990-2019 worldwide, while the ASRs of HIV-DS-TB and HIV-MDR-TB decreased after 2005. HIV-XDR-TB was a great threat to Eastern Europe for the largest number of new cases (792, 95% UI: 487-1167) and the highest ASR (0.34 per 100,000 population, 95% UI: 0.21-0.50). In addition, Oceania had the largest rise in ASRs of HIV-MDR-TB (EAPC = 22.56, 95% CI: 18.62-26.64) and HIV-XDR-TB (EAPC = 32.95, 95% CI: 27.90-38.20) during

1990-2019. Recently, age-specific incidence rates of HIV-XDR-TB increased in all age groups, especially in the 50-69 age groups among high, low-middle and low Socio-Demographic Index regions. Additionally, the proportion of patients aged <15 years was nearly 10% of new cases in sub-Saharan Africa in 2019, which was higher than in other regions.
CONCLUSIONS: HIV-infected drug-resistant TB is common in Oceania and Eastern Europe. Moreover, HIV-XDR-TB among elderly people became increasingly prevalent. In the future, the collaboration of management for HIV and TB should be intensified in Oceania and Eastern Europe, and more concerns need to be paid in elderly people.

DOI: 10.1080/23744235.2022.2092647
PMID: 35801264 [Indexed for MEDLINE]

41. **Selection bias in multidrug-resistant tuberculosis cohort studies assessing sputum culture conversion.**

PLoS One. 2022 Nov 10;17(11):e0276457. doi: 10.1371/journal.pone.0276457. eCollection 2022.

Rodriguez CA(1)(2), Lodi S(3), Horsburgh CR(1), Bastard M(4), Hewison C(5), Huerga H(4), Khan M(6), Khan PY(7)(8), Khan U(7), Oyewusi L(9), Padayachee S(6), Mitnick CD(2), Franke MF(2).

BACKGROUND: Conversion of sputum culture from positive to negative for M. tuberculosis is a key indicator of treatment response. An initial positive culture is a pre-requisite to observe conversion. Consequently, patients with a missing or negative initial culture are excluded from analyses of conversion outcomes. To identify the initial, or "baseline" culture, researchers must define a sample collection interval. An interval extending past treatment initiation can increase sample size but may introduce selection bias because patients without a positive pre-treatment culture must survive and remain in care to have a culture in the post-treatment interval.
METHODS: We used simulated data and data from the endTB observational cohort to investigate the potential for bias when extending baseline culture intervals past treatment initiation. We evaluated bias in the proportion with six-month conversion.
RESULTS: In simulation studies, the potential for bias depended on the proportion of patients missing a pre-treatment culture, proportion with conversion, proportion culture positive at treatment initiation, and proportion of patients missing a pre-treatment culture who would have been observed to be culture positive, had they had a culture. In observational data, the maximum potential for bias when reporting the proportion with conversion reached five

percentage points in some sites.
CONCLUSION: Extending the allowable baseline interval past treatment initiation may introduce selection bias. If investigators choose to extend the baseline collection interval past treatment initiation, the proportion missing a pre-treatment culture and the number of deaths and losses to follow up during the post-treatment allowable interval should be clearly enumerated.

DOI: 10.1371/journal.pone.0276457
PMCID: PMC9648724
PMID: 36355658 [Indexed for MEDLINE]

Conflict of interest statement: The endTB Consortium coordinated donations of delamanid (Otsuka Pharmaceutical) and bedaquiline (Janssen) to be used for treatment by some of the patients included in the endTB Observational Study. All authors report no additional potential conflicts of interest. This does not alter our adherence to PLOS ONE policies on sharing data and materials.

42. **CRISPR-Based Diagnostics: A Potential Tool to Address the Diagnostic Challenges of Tuberculosis.**

Pathogens. 2022 Oct 20;11(10):1211. doi: 10.3390/pathogens11101211.

Qi Y(1), Li K(2), Li Y(2), Guo D(2), Xu J(2), Li Y(1), Gong W(2).

Tuberculosis (TB) is an infectious disease caused by Mycobacterium tuberculosis, which infects more than 23% of the world's population. With the emergence of drug-resistant TB (DR-TB) and latent TB infection (LTBI), rapid diagnosis of DR-TB and LTBI has become a challenge for the prevention and control of TB. Herein, we highlight these challenges and discuss emerging clustered regularly interspaced short palindromic repeats (CRISPR)-based diagnostics in TB detection. Currently, the clinical diagnosis of M. tuberculosis infection mainly depends on pathogenic and molecular biological methods, including sputum smear, sputum culture, and Xpert. Although CRISPR-based diagnostics have not been applied to the clinical diagnosis of TB, they have shown exciting preponderances in TB diagnosis compared with traditional methods, including higher sensitivity, less sample input, and shorter turnaround time. CRISPR-based diagnostics represent a potential tool to address the challenges and natural weaknesses

associated with traditional TB diagnosis methods. Based on the currently available data, we suggest that future CRISPR-based TB diagnostics should be developed in the direction of automation, modularization, diversification, and intelligence. By combining the CRISPR platform with various systems, such as microfluidic chips, droplet microfluidics, electrochemical techniques, and optical systems, the specificity and sensitivity of TB diagnosis may be revolutionized.

DOI: 10.3390/pathogens11101211
PMCID: PMC9612056
PMID: 36297268

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

43. **A Dual Perspective of Psycho-Social Barriers and Challenges Experienced by Drug-Resistant TB Patients and Their Caregivers through the Course of Diagnosis and Treatment: Findings from a Qualitative Study in Bengaluru and Hyderabad Districts of South India.**

Antibiotics (Basel). 2022 Nov 10;11(11):1586. doi: 10.3390/antibiotics11111586.

Nagarajan K(1), Kumarsamy K(2), Begum R(2), Panibatla V(3), Reddy R(4), Adepu R(5), Munjattu JF(2), Sellapan S(6), Arangba S(1), Goswami A(7), Swamickan R(7), Muniyandi M(1).

Qualitative insights regarding psycho-social barriers and challenges experienced by drug-resistant tuberculosis (DR-TB) patients and their caregivers are understudied in India. We conducted a qualitative study using semi-structured qualitative interviews among treatment-completed DR-TB patients (n = 20) and caregivers (n = 20) in Bengaluru and Hyderabad districts, which represented two different socio-cultural settings in South India. Criterion sampling was used for recruiting the eligible participants who completed treatment with adherence. "Emotional issues and social barriers" were identified to represent a major challenge for patients and caregivers, which occurred acutely after disease diagnosis, characterized by fear and emotional distress due to their perceived loss of life prospects, severity of symptoms, discomfort, and disease denial. Medication intolerance, chronic symptoms, lack of visible signs of treatment progress, loss of weight, and physical concerns caused subsequent fear and distress during the treatment phases for patients along with experiences of stigma. External triggers generated "decisive moments" of hopelessness and

life-ending thoughts for patients at the diagnosis and early treatment phase. Medication related challenges included the perceived burden and power of pills which caused emotional distress for patients and intolerance towards caregivers. Pill burden was found as consequential as the side effects of injections. Challenges related to lack of support were another major theme, in which caregivers lacked resources for treatment support and nutrition. Throughout treatment, caregivers and patients expressed concern about a lack of supportive care from family members, sympathy, and intangible social support. Challenges during hospital admission in terms of lack of privacy, quality of services, individual attention, and empathy from health care workers were reported by patients and caregivers. Despite better adherence, DR-TB patients and caregivers experienced considerable emotional and social consequences. Differentiating DR-TB patients and caregivers' issues at different stages of diagnosis and treatment could help improve patient-centered outcomes in India and other high-burden nations.

DOI: 10.3390/antibiotics11111586
PMID: 36358241

44. **In silico evaluation of WHO-endorsed molecular methods to detect drug resistant tuberculosis.**

Sci Rep. 2022 Oct 22;12(1):17741. doi: 10.1038/s41598-022-21025-6.

Brankin A(1)(2), Seifert M(2)(3), Georghiou SB(2), Walker TM(1)(4), Uplekar S(2), Suresh A(2), Colman RE(5)(6).

Universal drug susceptibility testing (DST) for tuberculosis is a major goal of the END TB strategy. PCR-based molecular diagnostic tests have been instrumental in increasing DST globally and several assays have now been endorsed by the World Health Organization (WHO) for use in the diagnosis of drug resistance. These endorsed assays, however, each interrogate a limited number of mutations associated with resistance, potentially limiting their sensitivity compared to sequencing-based methods. We applied an in silico method to compare the sensitivity and specificity of WHO-endorsed molecular based diagnostics to the mutation set identified by the WHO mutations catalogue using phenotypic DST as the reference. We found that, in silico, the mutation sets used by probe-based molecular diagnostic tests to identify rifampicin, isoniazid, pyrazinamide, levofloxacin, moxifloxacin, amikacin, capreomycin and kanamycin resistance produced similar sensitivities and specificities to the WHO mutation catalogue. PCR-based diagnostic tests were most sensitive for drugs where mechanisms of resistance are well established and localised to small genetic regions or a few prevalent mutations. Approaches using sequencing technologies can provide

advantages for drugs where our knowledge of resistance is limited, or where complex resistance signatures exist.

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PMCID: PMC9587982
PMID: 36273016 [Indexed for MEDLINE]

Conflict of interest statement: A.B., M.S., S.B.G., S.U., A.S., R.E.C. are consultants or employees of FIND, the global alliance for diagnostics. T.M.W. declares no competing interests.

45. **Inequalities in the impact of COVID-19-associated disruptions on tuberculosis diagnosis by age and sex in 45 high TB burden countries.**

BMC Med. 2022 Nov 14;20(1):432. doi: 10.1186/s12916-022-02624-6.

McQuaid CF(#)(1), Henrion MYR(#)(2)(3), Burke RM(2)(4), MacPherson P(2)(3)(4), Nzawa-Soko R(2), Horton KC(5).

BACKGROUND: Tuberculosis remains a major public health priority and is the second leading cause of mortality from infectious disease worldwide. TB case detection rates are unacceptably low for men, the elderly and children. Disruptions in TB services due to the COVID-19 pandemic may have exacerbated these and other inequalities.
METHODS: We modelled trends in age- and sex- disaggregated case notifications for all forms of new and relapse TB reported to the World Health Organization for 45 high TB, TB/HIV and MDR-TB burden countries from 2013 to 2019. We compared trend predicted notifications to observed notifications in 2020 to estimate the number of people with TB likely to have missed or delayed diagnosis. We estimated the risk ratio (RR) of missed or delayed TB diagnosis for children (aged < 15 years) or the elderly (aged ≥ 65 years) compared to adults (aged 15-64 years) and women compared to men (both aged ≥ 15 years) using a random-effects meta-analysis.
RESULTS: An estimated 195,449 children (95% confidence interval, CI: 189,673-201,562, 37.8% of an expected 517,168), 1,126,133 adults (CI: 1,107,146-1,145,704, 21.8% of an expected 5,170,592) and 235,402 elderly (CI: 228,108-243,202, 28.5% of an expected 826,563) had a missed or delayed TB diagnosis in 2020. This included 511,546 women (CI: 499,623-523,869, 22.7%, of an expected 2,250,097) and 863,916 men (CI: 847,591-880,515, 23.0% of an expected 3,763,363). There was no evidence globally that the risk of having TB diagnosis missed or delayed was different for children and adults (RR: 1.09, CI:

0.41-2.91), the elderly and adults (RR: 1.40, CI: 0.62-3.16) or men and women (RR: 0.59, CI: 0.25-1.42). However, there was evidence of disparities in risk by age and/or sex in some WHO regions and in most countries.
CONCLUSIONS: There is no evidence at an aggregate global level of any difference by age or sex in the risk of disruption to TB diagnosis as a result of the COVID-19 pandemic. However, in many countries, disruptions in TB services have been greater for some groups than others. It is important to recognise these context-specific inequalities when prioritising key populations for catch-up campaigns.

DOI: 10.1186/s12916-022-02624-6
PMCID: PMC9660190
PMID: 36372899 [Indexed for MEDLINE]

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

46. **FDA-Approved Amoxapine Effectively Promotes Macrophage Control of Mycobacteria by Inducing Autophagy.**

Microbiol Spectr. 2022 Oct 26;10(5):e0250922. doi: 10.1128/spectrum.02509-22. Epub 2022 Sep 21.

Wang J(1), Sha J(1), Strong E(1), Chopra AK(1), Lee S(1).

Antibiotic resistance poses a significant hurdle in combating global public health crises, prompting the development of novel therapeutics. Strategies to enhance the intracellular killing of mycobacteria by targeting host defense mechanisms offer numerous beneficial effects, which include reducing cytotoxicity caused by current lengthy anti-tubercular treatment regimens and slowing or circumventing the development of multidrug-resistant strains. The intracellular pathogen Mycobacterium tuberculosis infects macrophages and exploits host machinery to survive and multiply. Using a cell-based screen of FDA-approved drugs, we identified an antidepressant, Amoxapine, capable of inhibiting macrophage cytotoxicity during mycobacterial infection. Notably, this reduced cytotoxicity was related to the enhanced intracellular killing of Mycobacterium bovis BCG and M. tuberculosis within human and murine macrophages. Interestingly, we discovered that postinfection treatment with Amoxapine inhibited mTOR (mammalian target of rapamycin) activation, resulting in the induction of autophagy without affecting autophagic flux in macrophages. Also, inhibition of autophagy by chemical inhibitor 3-MA or knockdown of an essential

component of the autophagic pathway, ATG16L1, significantly diminished Amoxapine's intracellular killing effects against mycobacteria in the host cells. Finally, we demonstrated that Amoxapine treatment enhanced host defense against M. tuberculosis in mice. In conclusion, our study identified Amoxapine as a novel host-directed drug that enhances the intracellular killing of mycobacteria by induction of autophagy, with concomitant protection of macrophages against death. IMPORTANCE The emergence and spread of multidrug-resistant (MDR) and extensive drug-resistant (XDR) TB urges the development of new therapeutics. One promising approach to combat drug resistance is targeting host factors necessary for the bacteria to survive or replicate while simultaneously minimizing the dosage of traditional agents. Moreover, repurposing FDA-approved drugs presents an attractive avenue for reducing the cost and time associated with new drug development. Using a cell-based screen of FDA-approved host-directed therapies (HDTs), we showed that Amoxapine inhibits macrophage cytotoxicity during mycobacterial infection and enhances the intracellular killing of mycobacteria within macrophages by activating the autophagy pathway, both in vitro and in vivo. These findings confirm targeted autophagy as an effective strategy for developing new HDT against mycobacteria.

DOI: 10.1128/spectrum.02509-22
PMCID: PMC9602717
PMID: 36129262 [Indexed for MEDLINE]

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

47. **Adenosine-Mimicking Derivatives of 3-Aminopyrazine-2-Carboxamide: Towards Inhibitors of Prolyl-tRNA Synthetase with Antimycobacterial Activity.**

Biomolecules. 2022 Oct 26;12(11):1561. doi: 10.3390/biom12111561.

Pallabothula VSK(1), Kerda M(1), Juhás M(1), Janďourek O(1), Konečná K(1), Bárta P(1), Paterová P(2), Zitko J(1).

Multidrug-resistant tuberculosis (MDR-TB) poses a significant threat to mankind and as such earned its place on the WHO list of priority pathogens. New antimycobacterials with a mechanism of action different to currently used agents are highly required. This study presents the design, synthesis, and biological evaluation of 3-acylaminopyrazine-2-carboxamides derived from a previously reported inhibitor of human prolyl-tRNA synthetase. Compounds were evaluated in vitro against various strains of mycobacteria, pathogenic bacteria, and fungi of clinical significance. In general, high activity against mycobacteria was noted, while the antibacterial and antifungal activity was minimal. The most active

compounds were 4'-substituted 3-(benzamido)pyrazine-2-carboxamides, exerting MIC (Minimum Inhibitory Concentration) from 1.95 to 31.25 μg/mL. Detailed structure-activity relationships were established and rationalized in silico with regard to mycobacterial ProRS as a probable target. The active compounds preserved their activity even against multidrug-resistant strains of Mycobacterium tuberculosis. At the same time, they were non-cytotoxic against HepG2 human hepatocellular carcinoma cells. This project is the first step in the successful repurposing of inhibitors of human ProRS to inhibitors of mycobacterial ProRS with antimycobacterial activity.

DOI: 10.3390/biom12111561
PMID: 36358911 [Indexed for MEDLINE]

48. **Determination of critical concentration for drug susceptibility testing of Mycobacterium tuberculosis against para-aminosalicylic acid with clinical isolates with thyA, folC and dfrA mutations.**

Ann Clin Microbiol Antimicrob. 2022 Nov 5;21(1):48. doi: 10.1186/s12941-022-00537-z.

Wang W(#)(1), Li S(#)(1), Ge Q(#)(2), Guo H(1), Shang Y(1), Ren W(1), Wang Y(3), Xue Z(3), Lu J(4), Pang Y(5).

BACKGROUND & OBJECTIVES: Accurate determination of antimicrobial resistance profiles is of great importance to formulate optimal regimens against multidrug-resistant tuberculosis (MDR-TB). Although para-aminosalicylic acid (PAS) has been widely used clinically, the reliable testing methods for PAS susceptibility were not established. Herein, we aimed to establish critical test concentration for PAS on the Mycobacterial Growth Indicator Tube (MGIT) 960 in our laboratory settings.
METHODS: A total of 102 clinical isolates were included in this study, including 82 wild-type and 20 resistotype isolates. Minimum inhibitory concentration (MIC) was determined by MGIT 960. Whole-genome sequencing was used to identify the mutation patterns potentially conferring PAS resistance. Sequence alignment and structure modelling were carried out to analyze potential drug-resistant mechanism of folC mutant.
RESULTS: Overall, the Minimum inhibitory concentration (MIC) distribution demonstrated excellent separation between wild-type and resistotype isolates. The wild-type population were all at least 1 dilution below 4 μg/ml, and the resistotype population were no lower than 4 μg/ml, indicating that 4 μg/ml was appropriate critical concentration to separate these two populations. Of 20 mutant isolates, 12 (60.0%) harbored thyA mutations, 2 (10%) had a mutation on upstream of dfrA, and the remaining isolates had folC mutations. Overall, thyA

and folC mutations were scattered throughout the whole gene without any one mutation predominating. All mutations within thyA resulted in high-level resistance to PAS (MIC > 32 μg/ml); whereas the MICs of isolates with folC mutations exhibited great diversity, ranged from 4 to > 32 μg/ml, and sequence and structure analysis partially provided the possible reasons for this diversity.
CONCLUSIONS: We propose 4 μg/ml as tentative critical concentration for MGIT 960. The major mechanism of PAS resistance is mutations within thyA and folC in MTB isolations. The whole-gene deletion of thyA locus confers high-level resistance to PAS. The diversity of many distinct mutations scattered throughout the full-length folC gene challenges the PCR-based mutation analysis for PAS susceptibility.

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PMCID: PMC9637297
PMID: 36335391 [Indexed for MEDLINE]

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

49. **Linezolid-related adverse effects in the treatment of rifampicin resistant tuberculosis: a retrospective study.**

J Chemother. 2022 Nov 2:1-7. doi: 10.1080/1120009X.2022.2136447. Online ahead of print.

Cui D(1), Hu X(2), Shi L(3), Wang D(4), Chen G(4).

Linezolid (LZD) is an effective drug in treating multidrug-resistant tuberculosis and extensively drug-resistant tuberculosis. This study aimed to evaluate the safety of LZD in the treatment of patients with rifampicin resistant tuberculosis. This was a multicenter retrospective study. A total of 184 patients of the rifampicin resistant tuberculosis patients treated with LZD from Jan 2018 to Apr 2020 in three hospitals were involved, and their clinical symptoms were recorded and analyzed. Meanwhile, the types and incidence of adverse effects associated with LZD were evaluated. It showed that peripheral neuritis (51, 27.7%) and hemochromatosis (42, 22.8%) were the most common adverse effects observed among these patients. The median time of symptoms after LZD treatment was 45.5 and 120.0 days, respectively. Furthermore, female patients had a significantly higher risk for leukopenia (P = 0.002) and hemochromatosis (P = 0.033) when compared with male patients. History of underlying disease was the risk factor for thrombocytopenia (P = 0.022).

Patients with long duration of medication (RR = 1.004, 95%CI: 1.002-1.006, P < 0.001) and daily dosage ≥600mg (RR = 3.059, 95%CI: 1.238-7.558, P = 0.015) were at higher risk of hemochromatosis. Age was the risk factor for rash (P = 0.008) and nausea and vomiting (P = 0.018). In addition, LZD administration time was the risk factor for optic neuritis (P < 0.001) and peripheral neuritis (P < 0.001). LZD can cause adverse symptoms in patients with rifampicin resistant tuberculosis. Gender, history of underlying disease, LZD use time, LZD dosage, and age are the risk factors in the LZD treatment of these patients. During medication, bone marrow suppression and neuropathy should be closely monitored. This study could potentially provide useful information for the clinical practice.

DOI: 10.1080/1120009X.2022.2136447
PMID: 36322121

50. **Design, synthesis and biological evaluation of (Quinazoline 4-yloxy)acetamide and (4-oxoquinazoline-3(4H)-yl)acetamide derivatives as inhibitors of Mycobacterium tuberculosis bd oxidase.**

Eur J Med Chem. 2022 Nov 15;242:114639. doi: 10.1016/j.ejmech.2022.114639. Epub 2022 Aug 6.

Kumar A(1), Kumari N(2), Bhattacherjee S(1), Venugopal U(2), Parwez S(3), Siddiqi MI(3), Krishnan MY(4), Panda G(5).

New chemical scaffolds with novel mechanism of action are urgently needed for the treatment of drug resistant tuberculosis. The oxidative phosphorylation pathway of Mycobacterium tuberculosis consists of multiple clinically validated drug targets. This pathway can function through any one of the two terminal oxidases-the proton pumping cytochrome bc1-aa3 supercomplex, or the less energy efficient but high affinity cytochrome bd oxidase. Inhibiting the bc1 complex alone has been found bacteriostatic and not bactericidal. On the other hand, inhibition of both these oxidases turns lethal to the pathogen. In the present study, we used a bc1 complex mutant of M. tuberculosis to screen (Quinazoline 4-yloxy)acetamide and (4-oxoquinazoline-3(4H)-yl)acetamide derivatives against the alternate oxidase, i.e., cytochrome bd oxidase. Two molecules, S-021-0601 and S-021-0607 were found to inhibit the mutant with MICs 8 and 16 μM respectively, compared to MICs of 128 and 256 μM against the wild type M. tuberculosis. In the wild type, one of the compounds showed synergism with Q203, an inhibitor of bc1 complex, in inhibiting growth under aerobic conditions. Both compounds showed synergism with Q203 in depleting bacterial ATP and inhibiting oxygen consumption. Both the compounds at 32 μM (one-fourth or one-eighth of their MICs for wild type) were bactericidal to wild type bacteria under hypoxic

condition, causing ~1.9 log10 reduction in viable counts which increased to ~4-log10 when combined with Q203.

DOI: 10.1016/j.ejmech.2022.114639
PMID: 35973312 [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. **An interesting case report of cutaneous tuberculosis of the foot.**

Int J Surg Case Rep. 2022 Nov;100:107763. doi: 10.1016/j.ijscr.2022.107763. Epub 2022 Oct 23.

Tharun Ganapathy C(1), George NM(2), Selvamuthukumaran S(1), Anguraj P(1), Gilani A(1).

INTRODUCTION AND IMPORTANCE: Tuberculosis is an age old disease caused by Mycobacterium tuberculosis which has been a menace to public health and thwarting economic growth. Pulmonary tuberculosis being the most common type, extra pulmonary tuberculosis has a greater association with HIV and multidrug resistant tuberculosis. Cutaneous tuberculosis accounts for 1-1.5 % of extra pulmonary tuberculosis.
CASE PRESENTATION: A 32 year old female presented to the outpatient department with a two month history of ulcer over the sole of the foot with multiple discharging sinuses and surrounding induration. Laboratory tests reported elevated total leukocyte counts. Magnetic Resonance Imaging of the foot showed diffuse intermuscular edema with an interconnecting sinus tract draining to the sole of the foot. Regular wound dressings and antibiotics showed no resolution. Patient eventually underwent near complete excision of the ulcer. The biopsy was suggestive of tuberculous etiology. She achieved complete resolution with antituberculous drugs by three months.
CLINICAL DISCUSSION: Cutaneous tuberculosis is often misdiagnosed as it can masquerade as many other commonly encountered dermatological conditions. Microbiological diagnosis plays a crucial role in the accurate diagnosis of cutaneous tuberculosis. These lesions are highly responsive to antituberculous drugs.
CONCLUSION: Cutaneous tuberculosis is a rare disease that should be considered in the differential diagnosis of patients with chronic non-healing wounds that

are poorly responsive to conventional treatment methods.

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PMCID: PMC9618970
PMID: 36308950

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

52. **Gender-related factors associated with delayed diagnosis of tuberculosis in Eastern Europe and Central Asia.**

BMC Public Health. 2022 Nov 1;22(1):1999. doi: 10.1186/s12889-022-14419-8.

Turusbekova N(1), Celan C(2), Caraulan L(3), Rucsineanu O(4), Jibuti M(5), Ibragimova O(6), Saidova N(7).

Tuberculosis (TB), a preventable and treatable disease, yearly affects millions of people and takes more than a million lives. Recognizing the symptoms and obtaining the correct diagnosis are vital steps towards treatment and cure. How timely a person with TB gets diagnosed may be influenced by biological differences between the sexes, and factors that are linked to the person's gender, in the context of the prevailing gender norms. According to our hypothesis, gender-related factors contribute to delays in the diagnosis of TB. We investigated four countries (Georgia, Kazakhstan, Republic of Moldova, and Tajikistan) of Eastern Europe and Central Asia (EECA) - a region with a high burden of drug-resistant TB, scarcity of gender-related TB information, and varying gender equality. Retrospective information was collected directly from the people with a history of TB - through in-depth interviews and focus group discussions. We did not find differences between genders in the way participants recognized TB symptoms. In three countries women de-prioritized seeking diagnosis because of their lack of access to finances, and household-related obligations. In all four countries, men, traditionally carrying the weight of economically supporting the family, tended to postpone TB diagnosis. In two countries women experienced stigma more often than men, and it was a deterrent factor to seeking healthcare. The role of gender in obtaining the correct diagnosis came forth only among the respondents from Georgia and to some extent from Kazakhstan. We conclude that there are barriers to health care seeking and TB diagnosis that affect differently women, men and gender-diverse persons in EECA Region.

DOI: 10.1186/s12889-022-14419-8
PMCID: PMC9623904
PMID: 36320011 [Indexed for MEDLINE]

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

53. **Whole-Genome Sequencing for Resistance Prediction and Transmission Analysis of Mycobacterium tuberculosis Complex Strains from Namibia.**

Microbiol Spectr. 2022 Oct 26;10(5):e0158622. doi: 10.1128/spectrum.01586-22. Epub 2022 Sep 27.

Claassens M(#)(1), Dreyer V(#)(2)(3), Nepolo E(#)(1), Mokomele Q(4), van Rooyen G(4), Ruswa N(5), Günther G(#)(1)(6)(7), Niemann S(#)(1)(2)(3).

Namibia is among 30 countries with a high burden of tuberculosis (TB), with an estimated incidence of 460 per 100,000 population and around 800 new multidrug-resistant (MDR) TB cases per year. Still, data on the transmission and evolution of drug-resistant Mycobacterium tuberculosis complex (Mtbc) strains are not available. Whole-genome sequencing data of 136 rifampicin-resistant (RIFr) Mtbc strains obtained from 2016 to 2018 were used for phylogenetic classification, resistance prediction, and cluster analysis and linked with phenotypic drug susceptibility testing (pDST) data. Roughly 50% of the strains investigated were resistant to all first-line drugs. Furthermore, 13% of the MDR Mtbc strains were already pre-extensively drug resistant (pre-XDR). The cluster rates were high, at 74.6% among MDR and 85% among pre-XDR strains. A significant proportion of strains had borderline resistance-conferring mutations, e.g., inhA promoter mutations or rpoB L430P. Accordingly, 25% of the RIFr strains tested susceptible by pDST. Finally, we determined a potentially new bedaquiline resistance mutation (Rv0678 D88G) occurring in two independent clusters. High rates of resistance to first-line drugs in line with emerging pre-XDR and likely bedaquiline resistance linked with the ongoing recent transmission of MDR Mtbc clones underline the urgent need for the implementation of interventions that allow rapid diagnostics to break MDR TB transmission chains in the country. A borderline RIFr mutation in the dominant outbreak strain causing discrepancies between phenotypic and genotypic resistance testing results may require breakpoint adjustments but also may allow individualized regimens with high-dose treatment. IMPORTANCE The transmission of drug-resistant tuberculosis (TB) is a

major problem for global TB control. Using genome sequencing, we showed that 13% of the multidrug-resistant (MDR) M. tuberculosis complex strains from Namibia are already pre-extensively drug resistant (pre-XDR), which is substantial in an African setting. Our data also indicate that the ongoing transmission of MDR and pre-XDR strains contributes significantly to the problem. In contrast to other settings with higher rates of drug resistance, we found a high proportion of strains having so-called borderline low-level resistance mutations, e.g., inhA promoter mutations or rpoB L430P. This led to the misclassification of 25% of the rifampicin-resistant strains as susceptible by phenotypic drug susceptibility testing. This observation potentially allows individualized regimens with high-dose treatment as a potential option for patients with few treatment options. We also found a potentially new bedaquiline resistance mutation in rv0678.

DOI: 10.1128/spectrum.01586-22
PMCID: PMC9603870
PMID: 36165641 [Indexed for MEDLINE]

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

54. **Predictors of sputum culture conversion time among MDR/RR TB patients on treatment in a low-income setting.**

PLoS One. 2022 Nov 14;17(11):e0277642. doi: 10.1371/journal.pone.0277642. eCollection 2022.

Meshesha MD(1).

OBJECTIVE: This study aimed to assess the time to first culture conversion and its predictors among MDR/RR-TB cases enrolled in Dilchora Hospital.
METHOD: A retrospective cohort study was conducted among MDR/RR TB cases enrolled between January 2014 and December 2018. SPSS version 26 was used for analysis. Reports are presented using percentages and frequency. Independent predictors of time-to-culture conversion were identified using multivariate Cox proportional hazard regression. Adjusted and crude hazard ratio with 95% CI was used. P-value< 0.05 declared statistical significance.
RESULT: A total of 145 MDR/RR TB cases were included. The median time to culture conversion was at 2 months. Higher baseline hemoglobin [AHR:1.101(1.02-1.19)] and having a non-cavitary lesion on chest x-ray[AHR:1.803(1.15-2.83)] predicted a higher likelihood of early culture conversion. Resistance to at least one first-line anti-TB drug in addition to rifampicin was associated with a lower hazard of early culture conversion as compared to only rifampicin resistance[AHR: 0.577(0.37-0.91)].

CONCLUSION & RECOMMENDATION: A baseline hemoglobin level, chest x-ray finding of cavitation and resistance to rifampicin, and at least one additional drug predicted the time to culture conversion. A closer treatment monitoring and follow-up should be emphasized for those presenting with lower baseline hemoglobin, more drug resistance, and cavitation on chest x-ray.

DOI: 10.1371/journal.pone.0277642
PMCID: PMC9662721
PMID: 36374857 [Indexed for MEDLINE]

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

56. **Significance of desmoplastic reactions on tumor deposits in patients with colorectal cancer.**

Oncol Lett. 2022 Nov 8;25(1):1. doi: 10.3892/ol.2022.13587. eCollection 2023 Jan.

Kobayashi T(1), Ishida M(2), Miki H(1), Hatta M(1), Hamada M(1)(3), Hirose Y(2), Sekimoto M(1).

It has been well recognized that the tumor microenvironment serves important roles in the progression and invasion of cancer. The desmoplastic reaction (DR) is a fibrous tissue reaction around tumor cells, and the prognostic significance of DR in colorectal cancer (CRC) has been established. Tumor deposits (TD) are also an important prognostic indicator of CRC. Notably, immature type DR has been linked to poor prognosis. In addition, immature type DR is significantly associated with a higher pT stage, presence of lymphovascular invasion and lymph node metastasis; however, to the best of our knowledge, the association between DR and TD has not yet been examined. The present study aimed to clarify this association. This study included 443 consecutive patients with pT3 or pT4 CRC who underwent surgical resection. The histopathological features, including DR and TD, were evaluated. Statistical analyses of the presence of TD, DR and other clinicopathological parameters were performed. The present cohort included 205 female and 238 male patients; 293 (66.1%) and 150 (33.9%) patients were classified as pT3 and pT4, respectively. Immature, intermediate and mature DR were noted in 282 (63.7%), 91 (20.5%) and 70 patients (15.8%), respectively. TD

was observed in 93 (21.0%) patients. Immature type DR was significantly associated with a higher pT stage (P<0.0001), presence of lymph node metastasis (P<0.0001), lymphatic (P=0.0007), venous (P<0.0001) and perineural invasion (P<0.0001), and higher tumor budding (TB) (P<0.0001). Moreover, immature type DR was significantly associated with the presence of TD (P<0.0001). The present study demonstrated a significant association between immature type DR and the presence of TD, and suggested a close relationship between lymphovascular invasion, DR, TB and TD. Additional studies are required to analyze the detailed mechanism underlying the development of immature DR in CRC to define novel treatment strategies.

DOI: 10.3892/ol.2022.13587
PMCID: PMC9677517
PMID: 36419753

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

57. **Mycobacterium tuberculosis Utilizes Host Histamine Receptor H1 to Modulate Reactive Oxygen Species Production and Phagosome Maturation via the p38MAPK-NOX2 Axis.**

mBio. 2022 Oct 26;13(5):e0200422. doi: 10.1128/mbio.02004-22. Epub 2022 Aug 24.

Mo S(#)(1)(2)(3), Guo J(#)(4), Ye T(5), Zhang X(1), Zeng J(6), Xu Y(7), Peng B(1), Dai Y(1), Xiao W(1), Zhang P(5), Deng G(5), Xu D(6), Long X(2)(3), Cai Y(1), Chen X(1).

Tuberculosis (TB), which is caused by the single pathogenic bacterium, Mycobacterium tuberculosis, is among the top 10 lethal diseases worldwide. This situation has been exacerbated by the increasing number of cases of multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB). Histamine is an organic nitrogenous compound that mediates a plethora of cell processes via different receptors. The expression of histamine receptor H1 (HRH1), one of the four histamine receptors identified to date was previously reported to be augmented by M. tuberculosis infection, although the underlying mechanism is unclear. In the present study, we applied confocal microscopy, flow cytometry, and Western blotting to show that HRH1 expression was enhanced in macrophages following mycobacterial infection. Furthermore, by combining techniques of gene knockdown, immunoprecipitation, intracellular bacterial burden analysis, fluorescence labeling, and imaging, we found that M.

tuberculosis targeted the host HRH1 to suppress NOX2-mediated cROS production and inhibit phagosome maturation and acidification via the GRK2-p38MAPK signaling pathway. Our findings clarified the underlying mechanism of the M. tuberculosis and host HRH1 interaction and may provide useful information for the development of novel antituberculosis treatments. IMPORTANCE Once engulfed in macrophage phagosomes, M. tuberculosis adopts various strategies to take advantage of the host environment for its intracellular survival. Histamine is an organic nitrogen-containing compound that mediates a plethora of cellular processes via different receptors, but the crosstalk mechanism between M. tuberculosis and HRH1 in macrophages is not clear. Our results revealed that M. tuberculosis infection enhanced HRH1 expression, which in turn restrained macrophage bactericidal activity by modulating the GRK2-p38MAPK signaling pathway, inhibiting NOX2-mediated cROS production and phagosome maturation. Clarification of the underlying mechanism by which M. tuberculosis utilizes host HRH1 to favor its intracellular survival may provide useful information for the development of novel antituberculosis treatments.

DOI: 10.1128/mbio.02004-22
PMCID: PMC9600773
PMID: 36000734 [Indexed for MEDLINE]

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

58. **Highly Sensitive Detection of Isoniazid Heteroresistance in Mycobacterium Tuberculosis by Droplet Digital PCR.**

Infect Drug Resist. 2022 Oct 28;15:6245-6254. doi: 10.2147/IDR.S381097. eCollection 2022.

Zheng Y(1), Xia H(1), Bao X(2), Zhao B(1), He P(1), Zhao Y(1).

PURPOSE: The drug resistance of Mycobacterium tuberculosis constitutes a major public health threat. Existing approaches make it challenging to detect low levels of drug-resistant TB, also known as heteroresistance (HR), in a population. The recently found droplet digital PCR (ddPCR) is a sensitive method for determining the precise amount of nucleic acid in a sample. We used ddPCR to test the Mycobacterium tuberculosis heteroresistance because it delivers more exact quantitative data without the need for a reference curve.
PATIENTS AND METHODS: A TaqMan-MGB probe mutation detection assay was developed in order to determine the mutant and wild-type sequences of the isoniazid resistance katG (315) gene. We produced heteroresistant MTB combinations, which were subsequently identified by ddPCR, qPCR, and MeltPro/INH. In addition, 21 clinical sputum samples with positive smears were used to validate each method's

capacity to determine HR in sputum.
RESULTS: We discovered that ddPCR can detect mutant sequences in as few as 0.01% of a combination. DeepMelt TB/INH, which is less sensitive in comparison, cannot detect HR with high resolution and requires a mutation rate of 50% to identify. qPCR likewise has a high resolution of 0.02%, but unlike ddPCR, it cannot determine the exact number of mutations. Our assay is applicable to sputum as well. ddPCR found a katG 315 substitution in two sputums with extremely low values of HR (0.26% and 0.14%). In 21 samples of clinical sputum, the HR prevalence of INH was 9.5%.
CONCLUSION: This work demonstrates that a well-designed ddPCR HR detection test can detect low levels of HR with high accuracy and consistency and gives new information for the clinical diagnosis of drug resistance.

DOI: 10.2147/IDR.S381097
PMCID: PMC9624153
PMID: 36329987

Conflict of interest statement: The authors state that there are no competing interests related to this study.

59. **NSC19723, a Thiacetazone-Like Benzaldehyde Thiosemicarbazone Improves the Efficacy of TB Drugs In Vitro and In Vivo.**

Microbiol Spectr. 2022 Oct 31:e0259222. doi: 10.1128/spectrum.02592-22. Online ahead of print.

Singh P(1), Rawat S(2), Agrahari AK(1), Singh M(1), Chugh S(1), Gurcha S(3), Singh A(3), Abrahams K(3), Besra GS(3), Asthana S(1), Rawat DS(2), Singh R(1).

The complexity and duration of tuberculosis (TB) treatment contributes to the emergence of drug resistant tuberculosis (DR-TB) and drug-associated side effects. Alternate chemotherapeutic agents are needed to shorten the time and improve efficacy of current treatment. In this study, we have assessed the antitubercular activity of NSC19723, a benzaldehyde thiosemicarbazone molecule. NSC19723 is structurally similar to thiacetazone (TAC), a second-line anti-TB drug used to treat individuals with DR-TB. NSC19723 displayed better MIC values than TAC against Mycobacterium tuberculosis and Mycobacterium bovis BCG. In our checkerboard experiments, NSC19723 displayed better profiles than TAC in combination with known first-line and recently approved drugs. Mechanistic studies revealed that NSC19723 inhibits mycolic acid biosynthesis by targeting the HadABC complex. Computational studies revealed that the binding pocket of

HadAB is similarly occupied by NSC19723 and TAC. NSC19723 also improved the efficacy of isoniazid in macrophages and mouse models of infection. Cumulatively, we have identified a benzaldehyde thiosemicarbazone scaffold that improved the activity of TB drugs in liquid cultures, macrophages, and mice. IMPORTANCE Mycobacterium tuberculosis, the causative agent of TB is among the leading causes of death among infectious diseases in humans. This situation has worsened due to the failure of BCG vaccines and the increased number of cases with HIV-TB coinfections and drug-resistant strains. Another challenge in the field is the lengthy duration of therapy for drug-sensitive and -resistant TB. Here, we have deciphered the mechanism of action of NSC19723, benzaldehyde thiosemicarbazone. We show that NSC19723 targets HadABC complex and inhibits mycolic acid biosynthesis. We also show that NSC19723 enhances the activity of known drugs in liquid cultures, macrophages, and mice. We have also performed molecular docking studies to identify the interacting residues of HadAB with NSC19723. Taken together, we demonstrate that NSC19723, a benzaldehyde thiosemicarbazone, has better antitubercular activity than thiacetazone.

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PMID: 36314972

60. **MmpL3 Inhibition as a Promising Approach to Develop Novel Therapies against Tuberculosis: A Spotlight on SQ109, Clinical Studies, and Patents Literature.**

Biomedicines. 2022 Nov 3;10(11):2793. doi: 10.3390/biomedicines10112793.

Imran M(1), Arora MK(2), Chaudhary A(3), Khan SA(4), Kamal M(5), Alshammari MM(6), Alharbi RM(7), Althomali NA(8), Alzimam IM(9), Alshammari AA(10), Alharbi BH(11), Alshengeti A(12)(13), Alsaleh AA(14), Alqahtani SA(15), Rabaan AA(16)(17)(18).

Tuberculosis (TB) is accountable for considerable global morbidity and mortality. Effective TB therapy with multiple drugs completes in about six months. The longer duration of TB therapy challenges patient compliance and contributes to treatment collapse and drug resistance (DR) progress. Therefore, new medications with an innovative mechanism of action are desperately required to shorten the TB therapy's duration and effective TB control. The mycobacterial membrane protein Large 3 (MmpL3) is a novel, mycobacteria-conserved and recognized promiscuous drug target used in the development of better treatments for multi-drug resistance TB (MDR-TB) and extensively drug-resistant TB (XDR-TB). This article spotlights MmpL3, the clinical studies of its inhibitor (SQ109), and the patent literature. The literature on MmpL3 inhibitors was searched on PubMed and freely available patent databases (Espacenet, USPTO, and PatentScope). SQ109, an analog of ethambutol (EMB), is an established MmpL3

inhibitor and has completed Phase 2b-3 clinical trials. Infectex and Sequella are developing orally active SQ109 in partnership to treat MDR pulmonary TB. SQ109 has demonstrated activity against drug-sensitive (DS) and drug-resistant (DR) Mycobacterium tuberculosis (Mtb) and a synergistic effect with isoniazid (INH), rifampicin (RIF), clofazimine (CFZ), and bedaquiline (BNQ). The combination of SQ109, clofazimine, bedaquiline, and pyrazinamide (PZA) has been patented due to its excellent anti-TB activity against MDR-TB, XDR-TB, and latent-TB. The combinations of SQ109 with other anti-TB drugs (chloroquine, hydroxychloroquine, and sutezolid) have also been claimed in the patent literature. SQ109 is more potent than EMB and could substitute EMB in the intensive stage of TB treatment with the three- or four-drug combination. Developing MmpL3 inhibitors is a promising approach to fighting the challenges associated with DS-TB and DR-TB. The authors foresee MmpL3 inhibitors such as SQ109 as future drugs for TB treatment.

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PMID: 36359313

61. **Multifaceted role of drugs: a potential weapon to outsmart Mycobacterium tuberculosis resistance by targeting its essential ThyX.**

J Biomol Struct Dyn. 2022 Nov;40(18):8508-8517. doi: 10.1080/07391102.2021.1913230. Epub 2021 Apr 16.

Tanweer S(1), Jamal S(1), Mehra S(1), Saqib N(1), Ahmad F(1), Faizan(1), Grover A(2), Grover S(1).

Tuberculosis (TB) is one of the prominent cause of deaths across the world and multidrug-resistant and extensively drug-resistant TB continues to pose challenges for clinicians and public health centers. The risk of death is extremely high in individuals who have compromised immune systems, HIV infection, or diabetes. Research institutes and pharmaceutical companies have been working on repurposing existing drugs as effective therapeutic options against TB. The identification of suitable drugs with multi-target affinity profiles is a widely accepted way to combat the development of resistance. Flavin-dependent thymidylate synthase (FDTS), known as ThyX, is in the class of methyltransferases and is a possible target in the discovery of novel anti-TB drugs. In this study, we aimed to repurpose existing drugs approved by Food and Drug Administration (FDA) that could be used in the treatment of TB. An integrated screening was performed based on computational procedures: high-throughput molecular docking techniques, followed by molecular dynamics simulations of the target enzyme, ThyX. After performing in silico screening using a library of 3,967 FDA-approved drugs, the two highest-scoring drugs,

Carglumic acid and Mesalazine, were selected as potential candidates that could be repurposed to treat TB.Communicated by Ramaswamy H. Sarma.

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62. **Prevalence, associated factors and rifampicin resistance pattern of pulmonary tuberculosis among HIV-positive patients attending antiretroviral treatment clinic at East Gojjam Zone, Ethiopia: An institution-based cross-sectional study.**

J Clin Tuberc Other Mycobact Dis. 2022 Nov 10;29:100336. doi: 10.1016/j.jctube.2022.100336. eCollection 2022 Dec.

Toru M(1), Baye A(1), Gebeyehu Z(1), Abebaw A(1), Reta A(1).

BACKGROUND: Drug-resistant tuberculosis (TB) threatens global TB care and prevention, and it remains a major public health concern in many countries particularly in sub-Saharan countries. Pulmonary TB is the most common serious opportunistic infection on HIV-positive patients and it is the leading cause of death among HIV-positive patients in developing countries. Ethiopia is one of the high TB burden countries with high morbidity and mortality.
OBJECTIVE: To determine the prevalence, associated factors and rifampicin resistance of pulmonary TB among HIV-positive attending antiretroviral treatment clinic at East Gojjam.
METHODS: Hospital-based cross-sectional study was conducted at Debre Markos Referral Hospital, from February to June 2019. A total of 112 HIV-positive TB suspected patients were included using convenient sampling techniques and a bacteriological confirmation test for tuberculosis was performed using Gene-Xpert MTB/RIF assay from a spot sputum sample. Viral load was determined by using a quantitative real-time polymerase chain reaction (RT-PCR) from the blood sample. Socio-demographic and clinical data were collected by face-to-face interview using a semi-structured questionnaire. The data were analyzed by using Statistical Package for Social Sciences (SPSS) software (version 24).
RESULT: Out of the 112 study participants, the prevalence of Pulmonary TB was 11.6 %. Among TB positives 23.1 % were rifampicin resistant. Rifampicin resistance was 100 % among female patients. Having family members treated for pulmonary TB (P = 0.003, [AOR = 4.5; 95 % CI = 3.59-58.8]), cigarette smoking (P = 0.039, [AOR = 2.18; 95 %CI = 1.17-40.5]), being on WHO HIV disease clinical stage II (P = 0.024, [AOR = 1.81; 95 %CI = 1.50-30.99]), and having viral load (1000-9999) RNA copies/ml (P = 0.031, [AOR = 1.54; 95 %CI = 1.32-31.41]) were found to be significantly associated with pulmonary TB.
CONCLUSION: The prevalence of pulmonary TB and rifampicin resistance was high

among HIV patients. Having family members treated for Pulmonary TB, history of cigarette smoking, WHO HIV clinical stage, and high viral load were associated risk factors for TB. Therefore, strengthening awareness creation on TB transmission, drug resistance, and treatment adherence are essential. Moreover, early screening and treatment are vital for preventing the transmission and occurrence of drug-resistant TB among study populations.

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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.

63. **Proteomic analysis of sequential isolates of multidrug-resistant Mycobacterium tuberculosis during treatment failure.**

J Infect. 2022 Nov;85(5):e137-e139. doi: 10.1016/j.jinf.2022.08.010. Epub 2022 Aug 17.

Lee DG(1), Kim HJ(2), Park MJ(3), Hong JH(2), Ryoo S(4).

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PMID: 35987390 [Indexed for MEDLINE]

Conflict of interest statement: Declaration of Competing Interest None.

64. **Making global health 'work': Frontline workers' labour in research and interventions.**

Glob Public Health. 2022 Nov 2:1-10. doi: 10.1080/17441692.2022.2139852. Online ahead of print.

Kingori P(1)(2), Kombe F(3)(4), Fehr A(5)(6).

This Special Issue of Global Public Health draws on the concept of 'body work' among those employed to support operationalising, researching, and implementing global health while in direct contact with the bodies of others. This collection brings into sharp focus the specific forms of labour of those occupying

positions as frontline workers - those who make global health work. Making Global Health Work includes authors from diverse backgrounds, disciplines, and geographies. Through compelling ethnographies, qualitative interviews, and focus group discussions, they explore 'body work' globally, including: Afghanistan, Bangladesh, Ethiopia, India, Indonesia, Kenya, Malawi, Myanmar, Nigeria, Nepal, Pakistan, Sierra Leone, South Sudan, Tanzania, Thailand, The Democratic Republic of the Congo (DRC), The Gambia, Vietnam, and Zimbabwe. These papers demonstrate that proximity to, and work on, the bodies of others engenders specific forms of (physical, emotional, mental, social, ethical, and political) labour, which occur not only in emergencies and pandemics, but also throughout the quotidian practice of global health. Making Global Health Work provides insights into the provision of maternal healthcare, treatment of multidrug resistant tuberculosis, rapid HIV testing programmes, sleeping sickness and polio eradication campaigns, mass drug administration clinical trials, epidemic preparedness and response, and the management and care of dead bodies. These papers argue for greater attention by global health actors on frontline workers in management of the complexities involved in making global health work.

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PMID: 36322777

66. **ECG monitoring in STREAM Stage 1: can we identify those at increased risk of QT prolongation?**

Int J Tuberc Lung Dis. 2022 Nov 1;26(11):1065-1070. doi: 10.5588/ijtld.22.0063.

Hughes G(1), Bern H(1), Chiang CY(2), Goodall RL(1), Nunn AJ(1), Rusen ID(3), Meredith SK(1).

BACKGROUND: STREAM (Standardised Treatment Regimen of Anti-tuberculosis Drugs for Patients with Multidrug-resistant Tuberculosis) Stage 1 was a randomised trial of a Short (9-month) regimen for rifampicin-resistant TB (RR-TB). QT or QTcF prolongation ≥500 ms occurred in 31 (11%) of 282 Short regimen participants. The frequent ECG monitoring employed might be challenging for treatment programmes. This analysis aimed to determine whether those at higher risk of severe QT prolongation could be identified early for more targeted monitoring.METHODS: Data from the first month of treatment were used to investigate whether participants were at risk of developing QT/QTcF ≥500 ms. QTcF increases from baseline at different time points were examined. Absolute QTcF measurements were categorised in 5 ms increments at each time-point. The most discriminating time points and QTcF cut-offs were combined to optimise sensitivity and specificity.RESULTS: Absolute QTcF values were more discriminating than magnitude of increase from baseline. More

participants who developed QT/QTcF ≥500 ms had a QTcF of respectively ≥425 ms and ≥430 ms at 4 h and Week 3 (P < 0.05) than those who did not. By combining QTcF values ≥425 ms at 4 h and ≥430 ms at Week 3, we identified high-risk participants with 97% sensitivity and 99% negative predictive value.CONCLUSION: Reduced ECG monitoring may be possible for many Short regimen participants.

DOI: 10.5588/ijtld.22.0063
PMID: 36281045 [Indexed for MEDLINE]

68. **Comparative Performance of Line Probe Assay and GeneXpert in the Detection of Rifampicin Monoresistance in a TB-Endemic African Country.**

Antibiotics (Basel). 2022 Oct 27;11(11):1489. doi: 10.3390/antibiotics11111489.

Mchaki BR(1)(2), Mgaya FX(2), Kunambi PP(2), Hang'ombe B(1), Matee MI(2), Munyeme M(1).

Rapid, accurate and reliable assays are required for timely detection of drug-resistant tuberculosis and early initiation of second-line TB treatment as well as to minimize transmission of resistant strains. This study assessed diagnostic performance characteristics of two rapid molecular assays, line probe assay (LPA) and GeneXpert (MTB/RIF), in the detection rifampicin monoresistance using the phenotypic proportion method on Lowenstein-Jensen media as the gold standard. This study involved a total of 357 isolates, 74 rifampicin-resistant and 283 rifampicin-susceptible, collected at the Central Tuberculosis Reference Laboratory (CTRL) in Dar es Salaam, Tanzania, between 2016 and 2019. Sensitivity, specificity and positive and negative predictive values were used to assess the performance characteristics of the two assays while kappa coefficient was used to determine agreement of test results. The receiver operating curve (ROC) was used to determine the discriminatory ability of the test in distinguishing resistant and susceptible TB isolates. Our results showed that GeneXpert had sensitivity, specificity and positive and negative predictive values of 93.2, 82.7, 58.5 and 97.9%, respectively; the corresponding performance for LPA was 86.5, 97.5, 90.1 and 96.5%, respectively. Compared with conventional phenotypic DST results, GeneXpert had a moderate agreement (kappa 0.621, p < 0.001), while LPA had high agreement (0.853, p < 0.001). LPA showed an accuracy of 95.2% compared to GeneXpert's 84.9%. ROC curve depicted the ability of the tests to distinguish rifampicin-sensitive and rifampicin-resistant strains to be 87.9% for GeneXpert and 92.0% for LPA. Our results indicate the superiority of LPA over GeneXpert regarding detection of rifampicin monoresistance. However, logistic challenges such as longer turnaround time and need for skilled laboratory personnel may limit its use.

DOI: 10.3390/antibiotics11111489
PMID: 36358145

69. **Mycobacterium kansasaii and Mycobacterium scrofulaceum dual pulmonary infection in an immunocompetent male: first report from India.**

Monaldi Arch Chest Dis. 2022 Nov 2. doi: 10.4081/monaldi.2022.2371. Online ahead of print.

Ganga RT(1), Sharma P(2), Pati SK(3), Behera AK(4), Reddy SK(5).

A 57-year-old farmer presented with chronic cough and recurrent hemoptysis, previously treated for sputum positive pulmonary tuberculosis. Referred to us for evaluation of drug resistant tuberculosis as his sputum was persistently positive for acid fast bacilli along with radiological worsening even after 6 months of antitubercular treatment. Bronchoalveolar lavage was done and he was diagnosed with a rare mixed non-tuberculous mycobacyteria (NTM) pulmonary infection despite no immune dysfunction. He was successfully treated with multidrug regimen of rifampicin, isoniazid, ethambutol and clarithromycin.

DOI: 10.4081/monaldi.2022.2371
PMID: 36325918

70. **Bedaquiline fumarate microemulsion: formulation optimization, rheological characterization and in vitro studies.**

Nanomedicine (Lond). 2022 Nov 23. doi: 10.2217/nnm-2022-0132. Online ahead of print.

Pardhi VP(1), Suthar T(1), Sharma A(2), Jain K(1).

Aim: Bedaquiline fumarate (BQF), an antitubercular drug, shows limited bioavailability due to solubility-limited intestinal absorption. In this research, the authors formulated a BQF-loaded microemulsion to improve BQF's oral bioavailability. Methods: Microemulsion was prepared by a spontaneous emulsification method and evaluated for thermodynamic stability, size, dispersibility, transmittance, rheology, microrheology, drug release, cytotoxicity and cellular uptake. Results: Microemulsion showed an average globule size of 26.50 ± 6.29 nm with spherical geometry and revealed gel-sol-gel behavior in microrheological studies. Cytotoxicity and cell uptake studies in Caco-2 cells showed that BQF microemulsion was cytocompatible at the highest

concentration of 500 μg/ml with significantly higher cellular uptake than control. Conclusion: The present study indicates that BQF microemulsion could be explored further for effective treatment of multidrug-resistant tuberculosis.

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