PubMed Open Access

1. Community perspective on child-friendly medications for drug-resistant TB: importance, priorities and advocacy.

Int J Tuberc Lung Dis. 2023 Sep 1;27(9):655-657. doi: 10.5588/ijtld.23.0164.

Viljoen L(1), Acaba J(2), Agbassi YJP(3), Beko B(4), Goslett C(5), Hoddinott G(1), Kumar B(6), Kumar RG(7), McKenna L(8), Moses G(3), Sachs T(1), Seidel S(9), von Delft A(10).

DOI: 10.5588/ijtld.23.0164
PMCID: PMC10443785
PMID: 37608482 [Indexed for MEDLINE]

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

2. Global treatment outcomes of extensively drug-resistant tuberculosis in adults: A systematic review and meta-analysis.

J Infect. 2023 Sep;87(3):177-189. doi: 10.1016/j.jinf.2023.06.014. Epub 2023 Jun 23.

Pedersen OS(1), Holmgaard FB(2), Mikkelsen MKD(2), Lange C(3), Sotgiu G(4), Lillebaek T(5), Andersen AB(6), Wejse CM(7), Dahl VN(8).

INTRODUCTION: Historically, extensively drug-resistant tuberculosis has been notoriously difficult to treat with devasting outcomes. As we are coming to the end of an era where the 2006 extensively drug-resistant tuberculosis definitions and old treatment regimens are being replaced, we aimed to estimate the proportion of extensively drug-resistant tuberculosis patients globally who achieved successful treatment outcomes.

METHODS: We conducted a systematic review of PubMed/MEDLINE, Scopus, Web of Science, and Embase from January 1, 2005, through April 3, 2023. Included studies reported WHO treatment outcomes, or adaptions hereof, for pre-extensively and/or extensively drug-resistant tuberculosis patients according to the 2006 WHO definition. Eligible studies included cohorts of at least 10 adults (aged>18 years) that were not pregnant. Using a random-effects model, we calculated pooled proportions of treatment outcomes and performed sensitivity and subgroup analyses. PROSPERO registration number: CRD42022340961.

RESULTS: Among 5056 studies reviewed, we identified 94 studies from 26 countries, involving 10,223 extensively drug-resistant tuberculosis patients.

The pooled proportion of successful treatment outcomes was 44.2% (95%CI: 38.3-50.3). Sensitivity analyses consistently produced similar estimates. A slight improvement in treatment outcomes was observed after 2013. Furthermore, 25 studies reported outcomes for 3564 individuals with pre-extensively drug-resistant tuberculosis, of which 63.3% achieved successful treatment (95%CI: 43.1-72.5).

CONCLUSION: Globally, the success rate of extensively drug-resistant tuberculosis treatment is 44.2%, far below the WHO's target rate of 75%. These results may serve as a reference for future studies assessing extensively drug-resistant tuberculosis treatment outcomes under the 2021 definition treated with better treatment regimens available. Comprehensive surveillance data of extensively drug-resistant tuberculosis outcomes from the whole world are desirable to monitor treatment progress.

DOI: 10.1016/j.jinf.2023.06.014
PMID: 37356629 [Indexed for MEDLINE]

Conflict of interest statement: Declaration of Competing Interest CL reports support for the present manuscript (e.g., funding and medical writing) from DZIF (German Center of Infection Research); consulting fees from a consultation service to Insmed, a company that produced liposomal amikacin as an inhalative suspension for the treatment of non-tuberculous mycobacteria pulmonary disease (outside of the scope of this work); speakers' honoraria from Insmed, Gilead, and Janssen (all outside of the scope of this work); is a member of the data safety board of trials from Médecins Sans Frontières (outside of the scope of this work); is supported by the German Center for Infection Research (DZIF); and acknowledges funding from the European Commission (anTBiotic EU-H2020 733079, ClicTB EDCTP2 RIA2017T-2030, stool4TB EDCTP2 RIAD2018–2511, and UNITE4TB EU-IMI 101007873). ABA and VND are members of the advisory board for Nordicinfu Care Denmark who distributes ARIKAYCE® (amikacin liposome inhalation suspension) for Insmed (outside of the scope of this work). All other authors declare no competing interests.

3. Genetic surveillance and outcomes of pyrazinamide and fluoroquinolones-resistant tuberculosis in Taiwan.

J Microbiol Immunol Infect. 2023 Sep 4:S1684-1182(23)00164-0. doi: 10.1016/j.jmii.2023.08.013. Online ahead of print.

Huang HT(1), Lin WH(1), Chan TH(1), Jou R(2).

BACKGROUND: Pyrazinamide (PZA) and fluoroquinolone (FQ), particularly moxifloxacin (MXF), are essential drugs in the World Health Organization (WHO) recommended short-course regimen to treat drug-susceptible tuberculosis (TB).

METHODS: To understand the extent of PZA and MXF susceptibility in general TB cases in Taiwan, we conducted retrospective analyses of 385 conservative Mycobacterium tuberculosis complex (MTBC) isolates identified from 4 TB laboratories in different regions of Taiwan. The case information was obtained from the TB registry. Genotypic drug susceptibility testing (DST) was performed by sequencing drug-resistance associated genes, PZA (pncA) and FQ (gyrA, and gyrB). Phenotypic DST was determined using the Bactec MGIT 960 system or the agar proportion method. Genotyping was carried out using spacer oligonucleotide typing.

RESULTS: In this study, 4.7% (18/385) cases' isolates harbored pncA mutations and 7.0% (27/385) cases' isolates harbored gyrA or gyrB mutation. Notably, pncA mutation was associated with Beijing family genotypes (P = 0.028), East African-Indian (EAI) genotypes (P = 0.047) and MDR-TB (P < 0.001). Whereas, gyrA or gyrB mutation was associated with EAI genotypes (P = 0.020) and MDR-TB (P = 0.006). In addition, a statistically significant difference was found between the favorable outcomes using active and inactive PZA (P = 0.009) in 38 case isolates with any pncA, gyrA, or gyrB mutation.

CONCLUSION: We concluded that routine PZA and FQ susceptibility tests are recommended for guiding the treatment of TB.

DOI: 10.1016/j.jmii.2023.08.013
PMID: 37690869

Conflict of interest statement: Declaration of competing interest None.

4. Outbreak of Multidrug-Resistant Tuberculosis - Kansas, 2021-2022.

MMWR Morb Mortal Wkly Rep. 2023 Sep 1;72(35):957-960. doi: 10.15585/mmwr.mm7235a4.

Groenweghe E, Swensson L, Winans KD, Griffin P, Haddad MB, Brostrom RJ, Tuckey D, Lam CK, Armitige LY, Seaworth BJ, Corriveau EA.

An outbreak of multidrug-resistant (MDR) tuberculosis (TB) involved 13 persons in four households in a low-income, under-resourced urban Kansas community

during November 2021-November 2022. A majority of the seven adults identified in the Kansas outbreak were born outside the United States in a country that had experienced an MDR TB outbreak with the same genotype during 2007-2009, whereas most of the six children in the Kansas outbreak were U.S.-born. Prompt identification, evaluation, and treatment of persons with MDR TB and their contacts is essential to limiting transmission.

DOI: 10.15585/mmwr.mm7235a4
PMID: 37651293 [Indexed for MEDLINE]

Conflict of interest statement: All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. Barbara J. Seaworth reports consultant fees from Wyandotte County, Kansas for complicated tuberculosis (TB) patient management paid to the University of Texas at Tyler Health Science Center and serving as an uncompensated co-chair of the Community Research Advisory Group for CDC's Tuberculosis Trials Consortium. Erin A. Corriveau reports speaking at Pacific Islands Tuberculosis Controllers Association Conference about the current outbreak and the Kansas City TB program and funding from the Heartland National Tuberculosis Center to attend the Pacific Islands Tuberculosis Controllers Association conference. Lisa Y. Armitige reports receipt of an honorarium from the American Academy of HIV Medicine for writing a chapter, and participation on the Advisory Counsel for the Elimination of Tuberculosis (2014–2021). Kimberly D. Winans reports funding from Heartland National Tuberculosis Center and travel reimbursement from the Kansas Department of Health and Environment. No other potential conflicts of interest were disclosed.

5. Assessment of drug-susceptible and multidrug-resistant tuberculosis (MDR-TB) in the Central Region of Somalia: A 3-year retrospective study.

PLOS Glob Public Health. 2023 Sep 7;3(9):e0002319. doi: 10.1371/journal.pgph.0002319. eCollection 2023.

Mohamed MA(1)(2), Ali OA(3), Osman AM(4)(5)(6), Abatcha MG(7), Ahmed AA(2), Ali AM(8), Dirie AA(1), de Oliveira CJB(9)(10), Osman AY(1)(11), Wang SH(10)(12), Vieira RFC(13)(14).

BACKGROUND: Multidrug-resistant tuberculosis (MDR-TB) remains a public health emergency and a threat globally. Although increasing MDR-TB cases have been recently reported in Somalia, limited information is known. This study aims to determine the prevalence of drug-susceptible and MDR-TB in suspected patients referred to the TB Department in Mudug Hospital, Galkayo, Somalia, and identify potential factors associated with MDR-TB.

METHODS: A 3-year hospital laboratory-based retrospective study was conducted by manually reviewing laboratory records of Mycobacterium tuberculosis specimens and GeneXpert MTB/RIF results from January 2019 to December 2021 at the reference mycobacteria laboratory department in Mudug Hospital.

RESULTS: A total of 714 positive GeneXpert-MTB results were identified: 619 (86.7%) were drug susceptible (no Rifampin resistance [RR] detected) and 95 (13.3%) with RR detected or defined as MDR-TB. Most of the MDR-TB patients were males (71.6%, 68/95) and between the ages of 15 to 24 (31.6%, 30/95). Most isolates were collected in 2021 (43.2%, 41/95). Multivariate analyses show no significant difference between patients having MDR-TB and/or drug-susceptible TB for all variables.

CONCLUSION: This study showed an alarming frequency of MDR-TB cases among M. tuberculosis-positive patients at a regional TB reference laboratory in central Somalia.

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PMCID: PMC10484424
PMID: 37676848

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

6. Deciphering the emerging role of phytocompounds: Implications in the management of drug-resistant tuberculosis and ATDs-induced hepatic damage.

J Infect Public Health. 2023 Sep;16(9):1443-1459. doi: 10.1016/j.jiph.2023.07.016. Epub 2023 Jul 26.

Ansari MA(1), Shoaib S(2), Alomary MN(3), Ather H(4), Ansari SMA(5), Hani U(6), Jamous YF(7), Alyahya SA(8), Alharbi JN(9), Imran MA(10), Wahab S(11), Ahmad W(12), Islam N(13).

Tuberculosis is a disease of poverty, discrimination, and socioeconomic burden. Epidemiological studies suggest that the mortality and incidence of tuberculosis are unacceptably higher worldwide. Genomic mutations in embCAB, embR, katG,

inhA, ahpC, rpoB, pncA, rrs, rpsL, gyrA, gyrB, and ethR contribute to drug resistance reducing the susceptibility of Mycobacterium tuberculosis to many antibiotics. Additionally, treating tuberculosis with antibiotics also poses a serious risk of hepatotoxicity in the patient's body. Emerging data on drug-induced liver injury showed that anti-tuberculosis drugs remarkably altered levels of hepatotoxicity biomarkers. The review is an attempt to explore the anti-mycobacterial potential of selected, commonly available, and well-known phytocompounds and extracts of medicinal plants against strains of Mycobacterium tuberculosis. Many studies have demonstrated that phytocompounds such as flavonoids, alkaloids, terpenoids, and phenolic compounds have antibacterial action against Mycobacterium species, inhibiting the bacteria's growth and replication, and sometimes, causing cell death. Phytocompounds act by disrupting bacterial cell walls and membranes, reducing enzyme activity, and interfering with essential metabolic processes. The combination of these processes reduces the overall survivability of the bacteria. Moreover, several phytochemicals have synergistic effects with antibiotics routinely used to treat TB, improving their efficacy and decreasing the risk of resistance development. Interestingly, phytocompounds have been presented to reduce isoniazid- and ethambutol-induced hepatotoxicity by reversing serum levels of AST, ALP, ALT, bilirubin, MDA, urea, creatinine, and albumin to their normal range, leading to attenuation of inflammation and hepatic necrosis. As a result, phytochemicals represent a promising field of research for the development of new TB medicines.

DOI: 10.1016/j.jiph.2023.07.016
PMID: 37523915 [Indexed for MEDLINE]

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

7. Successful outcomes for patients with drug-resistant tuberculosis despite civil unrest and COVID-19 in Haiti.

PLOS Glob Public Health. 2023 Sep 12;3(9):e0002356. doi: 10.1371/journal.pgph.0002356. eCollection 2023.

Vilbrun SC(1), Souroutzidis A(2), Walsh KF(3)(4), Ellis J(5), Guiteau C(1), Delva S(1), Joissaint G(1), Joseph P(1), Pape JW(1)(3), Koenig SP(6).

Globally, treatment outcomes for people with multi-drug/rifampin-resistant tuberculosis (MDR/RR-TB) are sub-optimal, with MDR/RR-TB programs further weakened due to the COVID-19 pandemic, and in Haiti, by severe civil unrest. We

assessed the impact of these disruptions on treatment outcomes at GHESKIO, in Port-au-Prince, Haiti. We conducted a retrospective analysis including all adults (age ≥18 years) who initiated MDR/RR-TB treatment at GHESKIO from 2010 to 2020. We assessed predictors of poor treatment outcome using multivariable logistic regression, adjusting for baseline characteristics and year of treatment. 453 patients initiated treatment for MDR/RR-TB at GHESKIO. Median age was 31 (IQR: 25, 40), 233 (51.4%) were male, and 100 (22.1%) were living with HIV. Three hundred sixty-nine patients (81.5%) achieved cure, 42 (9.3%) died, 40 (8.8%) were lost to follow-up and 2 (<1%) failed treatment. HIV status was associated with poor treatment outcome (aRR: 1.65 (95% CI: 1.09, 2.48)) but there was no difference by year of treatment initiation. Outcomes for patients with MDR/RR-TB remained outstanding, even during the COVID-19 pandemic and severe civil unrest in Haiti. We attribute this resilience in care to the adaptability of program staff and provision of economic and psychosocial support.

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PMCID: PMC10497149
PMID: 37698996

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

8. Risk factors for multidrug-resistant tuberculosis in the Central African Republic: A case-control study.

J Infect Public Health. 2023 Sep;16(9):1341-1345. doi: 10.1016/j.jiph.2023.06.007. Epub 2023 Jun 13.

de Dieu Longo J(1), Woromogo SH(2), Tekpa G(3), Diemer HS(4), Gando H(5), Djidéré FA(5), Grésenguet G(1).

BACKGROUND: The emergence and spread of multidrug-resistant tuberculosis (MDR-TB) presents a challenge to the "End TB by 2035" strategy. This study aimed to identify the risk factors associated with MDR-TB in patients admitted to the pneumo-physiology clinic of the National University Hospital of Bangui in Central African Republic.

METHODS: This was a "retrospective" chart review study. Cases were represented by patients more than 18 years of age treated for MDR-TB and controls were patients with "at least rifampicin-susceptible" TB treated "with first-line anti-TB regimen" and who at the end of treatment were declared cured. The status of "cured" was exclusively applicable to non-MDR TB. Risk factors associated with MDR-TB were identified by multivariate analysis.

RESULTS: We included 70 cases and 140 controls. The median age was 35 years, IQR (22;46 years). The main factors associated with the occurrence of MDR-TB in multivariate analysis were male gender (0 R = 3.02 [1.89-3.99], p = 0.001), residence in a peri-urban/urban area (0 R = 3.06 [2.21-4.01], p = 0.002), history of previous TB treatment (0 R= 3.99 [2.77-4.25], p < 0.001) and the presence of multidrug-resistant TB in the family (0 R=1.86 [1.27-2.45], p = 0.021).

CONCLUSION: The emergence of MDR-TB can be reduced by implementing appropriate strategies, such as preventive therapy in contacts of MDR-TB patients and detecting and appropriately treating MDR-TB patients to prevent further spread of infection.

DOI: 10.1016/j.jiph.2023.06.007
PMID: 37437428 [Indexed for MEDLINE]

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

9. Analysis of Drug-Resistance Characteristics and Genetic Diversity of Multidrug-Resistant Tuberculosis Based on Whole-Genome Sequencing on the Hainan Island, China.

Infect Drug Resist. 2023 Sep 4;16:5783-5798. doi: 10.2147/IDR.S423955. eCollection 2023.

Wang J(#)(1), Yu C(#)(1), Xu Y(#)(1), Chen Z(1), Qiu W(1), Chen S(1), Pei H(1), Zhong Y(1).

PURPOSE: Given the high burden of Tuberculosis (TB) in China, the prevalence of multidrug-resistant tuberculosis (MDR-TB) is significant. Whole-genome sequencing (WGS) of Mycobacterium tuberculosis (MTB) enables the identification of lineages, drug-resistant mutations, and transmission patterns, offering valuable insights for TB control, clinical diagnosis, and treatment.

METHODS: We collected 202 MDR-MTB strains from 3519 suspected pulmonary TB patients treated at The Second Affiliated Hospital of Hainan Medical University between July 2019 and June 2021. Proportional drug-susceptibility testing was performed using 8 common anti-tuberculosis drugs. Subsequently, the genotypic drug resistance and genetic characteristics were analyzed by the WGS.

RESULTS: Lineages are identified by TB-profiler revealed 202 MDR-MTB strains, showcasing three predominant lineages, with lineage 2 being the most prevalent. Close genomic relatedness analysis and evidence of MTB transmission led to the formation of 15 clusters comprising 42 isolates, resulting in a clustering rate of 20.8%. Novelty, lineage 2.1 (non-Beijing) accounted for 27.2% of the MDR-MTB strains, which is rare in China and Neighboring countries. Regarding first-line anti-TB drugs, genes associated with rifampicin resistance, primarily the rpoB gene, were detected in 200 strains (99.0%). Genes conferring resistance to isoniazid, ethambutol, and streptomycin were identified in 191 (94.5%), 125 (61.9%), and 100 (49.5%) strains, respectively. Among the second-line drugs, 97 (48.0%) strains exhibited genes encoding resistance to fluoroquinolones. Comparing the results to phenotypic drug susceptibility-based testing, the sensitivity of WGS for detecting resistance to each of the six drugs (rifampicin, isoniazid, ethambutol, ofloxacin, kanamycin, capreomycin) was 90% or higher. With the exception of ethambutol, the specificity of WGS prediction for the remaining drugs exceeded 88%.

CONCLUSION: Our study provides crucial insights into genetic mutation types, genetic diversity, and transmission of MDR-MTB on Hainan Island, serving as a significant reference for MDR-MTB surveillance and clinical decision-making.

DOI: 10.2147/IDR.S423955
PMCID: PMC10487742
PMID: 37692467

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

10. Lineage classification and antitubercular drug resistance surveillance of Mycobacterium tuberculosis by whole-genome sequencing in Southern India.

Microbiol Spectr. 2023 Sep 6:e0453122. doi: 10.1128/spectrum.04531-22. Online ahead of print.

Rao M(#)(1), Wollenberg K(#)(2), Harris M(#)(2), Kulavalli S(1), Thomas L(1), Chawla K(3), Shenoy VP(3), Varma M(4), Saravu K(4), Hande HM(5), Shanthigrama Vasudeva CS(6), Jeffrey B(2), Gabrielian A(2), Rosenthal A(2).

Whole-genome sequencing has created a revolution in tuberculosis management by providing a comprehensive picture of the various genetic polymorphisms with unprecedented accuracy. Studies mapping genomic heterogeneity in clinical isolates of Mycobacterium tuberculosis using a whole-genome sequencing approach from high tuberculosis burden countries are underrepresented. We report whole-genome sequencing results of 242 clinical isolates of culture-confirmed M. tuberculosis isolates from tuberculosis patients referred to a tertiary care hospital in Southern India. Phylogenetic analysis revealed that the isolates in our study belonged to five different lineages, with Indo-Oceanic (lineage 1, n = 122) and East-African Indian (lineage 3, n = 80) being the most prevalent. We report several mutations in genes conferring resistance to first and second line antitubercular drugs including the genes rpoB, katG, ahpC, inhA, fabG1, embB, pncA, rpsL, rrs, and gyrA. The majority of these mutations were identified in relatively high proportions in lineage 1. Our study highlights the utility of whole-genome sequencing as a potential supplemental tool to the existing genotypic and phenotypic methods, in providing expedited comprehensive surveillance of mutations that may be associated with antitubercular drug resistance as well as lineage characterization of M. tuberculosis isolates. Further larger-scale whole-genome datasets with linked minimum inhibition concentration testing are imperative for resolving the discrepancies between whole-genome sequencing and phenotypic drug sensitivity testing results and quantifying the level of the resistance associated with the mutations for optimization of antitubercular drug and precise dose selection in clinics. IMPORTANCE Studies mapping genetic heterogeneity of clinical isolates of M. tuberculosis for determining their strain lineage and drug resistance by whole-genome sequencing are limited in high tuberculosis burden settings. We carried out whole-genome sequencing of 242 M. tuberculosis isolates from drug-sensitive and drug-resistant tuberculosis patients, identified and collected as part of the TB Portals Program, to have a comprehensive insight into the genetic diversity of M. tuberculosis in Southern India. We report several genetic variations in M. tuberculosis that may confer resistance to antitubercular drugs. Further wide-scale efforts are required to fully characterize M. tuberculosis genetic diversity at a population level in high tuberculosis burden settings for providing precise tuberculosis treatment.

DOI: 10.1128/spectrum.04531-22
PMID: 37671895

11. Evaluation of genetic mutations associated with phenotypic resistance to

fluoroquinolones, bedaquiline, and linezolid in clinical Mycobacterium tuberculosis: A systematic review and meta-analysis.

J Glob Antimicrob Resist. 2023 Sep;34:214-226. doi: 10.1016/j.jgar.2023.05.001. Epub 2023 May 11.

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

OBJECTIVES: The aim of the study was to update the classification of drugs used in multidrug-resistant tuberculosis (MDR-TB) regimens. Group A drugs (fluoroquinolones, bedaquiline (BDQ), and linezolid (LZD)) are crucial drugs for the control of MDR-TB. Molecular drug resistance assays could facilitate the effective use of Group A drugs.

METHODS: We summarised the evidence implicating specific genetic mutations in resistance to Group A drugs. We searched PubMed, Embase, MEDLINE, and the Cochrane Library for studies published from the inception of each database until July 1, 2022. Using a random-effects model, we calculated the odds ratios and 95% confidence intervals as our measures of association.

RESULTS: A total of 5001 clinical isolates were included in 47 studies. Mutations in gyrA A90V, D94G, D94N, and D94Y were significantly associated with an increased risk of a levofloxacin (LFX)-resistant phenotype. In addition, mutations in gyrA G88C, A90V, D94G, D94H, D94N, and D94Y were significantly associated with an increased risk of a moxifloxacin (MFX)-resistant phenotype. In only one study, the majority of gene loci (n = 126, 90.65%) in BDQ-resistant isolates were observed to have unique mutations in atpE, Rv0678, mmpL5, pepQ, and Rv1979c. The most common mutations occurred at four sites in the rrl gene (g2061t, g2270c, g2270t, and g2814t) and at one site in rplC (C154R) in LZD-resistant isolates. Our meta-analysis demonstrated that there were no mutations associated with BDQ- or LZD-resistant phenotypes.

CONCLUSION: The mutations detected by rapid molecular assay were correlated with phenotypic resistance to LFX and MFX. The absence of mutation-phenotype associations for BDQ and LZD hindered the development of a rapid molecular assay.

DOI: 10.1016/j.jgar.2023.05.001
PMID: 37172764 [Indexed for MEDLINE]

12. Formulation and Scale-up of Delamanid Nanoparticles via Emulsification for Oral

Tuberculosis Treatment.

Mol Pharm. 2023 Sep 4;20(9):4546-4558. doi: 10.1021/acs.molpharmaceut.3c00240. Epub 2023 Aug 14.

Caggiano NJ(1), Armstrong MS(1), Georgiou JS(1), Rawal A(2), Wilson BK(1), White CE(3)(4), Priestley RD(1)(5), Prud'homme RK(1).

Delamanid (DLM) is a hydrophobic small molecule therapeutic used to treat drug-resistant tuberculosis (DR-TB). Due to its hydrophobicity and resulting poor aqueous solubility, formulation strategies such as amorphous solid dispersions (ASDs) have been investigated to enhance its aqueous dissolution kinetics and thereby improve oral bioavailability. However, ASD formulations are susceptible to temperature- and humidity-induced phase separation and recrystallization under harsh storage conditions typically encountered in areas with high tuberculosis incidence. Nanoencapsulation represents an alternative formulation strategy to increase aqueous dissolution kinetics while remaining stable at elevated temperature and humidity. The stabilizer layer coating the nanoparticle drug core limits the formation of large drug domains by diffusion during storage, representing an advantage over ASDs. Initial attempts to form DLM-loaded nanoparticles via precipitation-driven self-assembly were unsuccessful, as the trifluoromethyl and nitro functional groups present on DLM were thought to interfere with surface stabilizer attachment. Therefore, in this work, we investigated the nanoencapsulation of DLM via emulsification, avoiding the formation of a solid drug core and instead keeping DLM dissolved in a dichloromethane dispersed phase during nanoparticle formation. Initial emulsion formulation screening by probe-tip ultrasonication revealed that a 1:1 mass ratio of lecithin and HPMC stabilizers formed 250 nm size-stable emulsion droplets with 40% DLM loading. Scale-up studies were performed to produce nearly identical droplet size distribution at larger scale using high-pressure homogenization, a continuous and industrially scalable technique. The resulting emulsions were spray-dried to form a dried powder, and in vitro dissolution studies showed dramatically enhanced dissolution kinetics compared to both as-received crystalline DLM and micronized crystalline DLM, owing to the increased specific surface area and partially amorphous character of the DLM-loaded nanoparticles. Solid-state NMR and dissolution studies showed good physical stability of the emulsion powders during accelerated stability testing (50 °C/75% RH, open vial).

DOI: 10.1021/acs.molpharmaceut.3c00240
PMCID: PMC10481377
PMID: 37578286 [Indexed for MEDLINE]

Conflict of interest statement: The authors declare no competing financial

interest.

13. Phenotypic and genotypic drug susceptibility patterns of Mycobacterium tuberculosis isolates from pulmonary tuberculosis patients in Central and Southern Ethiopia.

PLoS One. 2023 Sep 8;18(9):e0285063. doi: 10.1371/journal.pone.0285063. eCollection 2023.

Tilahun M(1)(2), Wegayehu T(1), Wondale B(1), Gebresilase TT(2), Gebreyohannes T(2), Tekola A(2), Alemu M(2), Neway S(2), Adnew B(2), Nassir MF(2), Kassahun Y(2), Aseffa A(2), Bobosha K(2).

INTRODUCTION: The persistence of tuberculosis (TB) infection in some patients after treatment has highlighted the importance of drug susceptibility testing (DST). This study aimed to determine the drug susceptibility patterns of Mycobacterium tuberculosis (M. tuberculosis) isolates from pulmonary TB (PTB) patients in Central and Southern Ethiopia.
METHODS: A health institution-based cross-sectional study was conducted between July 2021 and April 2022. Sputum samples were collected from newly diagnosed smear microscopy and/or Xpert MTB/RIF-positive PTB patients. The samples were processed and cultivated in Lowenstein-Jensen (LJ) pyruvate and glycerol medium. M. tuberculosis isolates were identified using polymerase chain reaction (PCR) based region of difference 9 (RD9) deletion typing. Phenotypic DST patterns of the isolates were characterized using the BACTEC MGIT™ 960 instrument with SIRE kit. Isoniazid (INH) and Rifampicin (RIF) resistant M. tuberculosis isolates were identified using the GenoType® MTBDRplus assay.
RESULTS: Sputum samples were collected from 350 PTB patients, 315 (90%) of which were culture-positive, and phenotypic and genotypic DST were determined for 266 and 261 isolates, respectively. Due to invalid results and missing data, 6% (16/266) of the isolates were excluded, while 94% (250/266) were included in the paired analysis. According to the findings, 14.4% (36/250) of the isolates tested positive for resistance to at least one anti-TB drug. Gene mutations were observed only in the rpoB and katG gene loci, indicating RIF and high-level INH resistance. The GenoType® MTBDRplus assay has a sensitivity of 42% and a specificity of 100% in detecting INH-resistant M. tuberculosis isolates, with a kappa value of 0.56 (95%CI: 0.36-0.76) compared to the BACTEC MGIT™ DST. The overall discordance between the two methods was 5.6% (14/250) for INH alone and 0% for RIF resistance and MDR-TB (resistance to both INH and RIF) detection.
CONCLUSION: This study reveals a higher prevalence of phenotypic and genotypic discordant INH-resistant M. tuberculosis isolates in the study area. The use of whole-genome sequencing (WGS) is essential for gaining a comprehensive understanding of these discrepancies within INH-resistant M. tuberculosis

strains.

DOI: 10.1371/journal.pone.0285063
PMCID: PMC10491001
PMID: 37682820 [Indexed for MEDLINE]

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

14. Difficulty in diagnosing peritonitis caused by multidrug-resistant tuberculosis.

Clin Case Rep. 2023 Aug 29;11(9):e7759. doi: 10.1002/ccr3.7759. eCollection 2023 Sep.

Aoyama S(1), Yamashita S(2), Ishizuka K(3), Katsukura S(4), Matsuura H(5), Kato M(6).

KEY CLINICAL MESSAGE: The low sensitivity of ascites culture for acid-fast bacilli necessitates a peritoneal biopsy when tuberculous peritonitis is suspected. Findings in the peritoneum on computed tomography may prompt suspicion of tuberculous peritonitis.
ABSTRACT: A 47-year-old Nigerian man presented with fever, abdominal distention, and weight loss. Abdominal computed tomography revealed massive ascites and peritoneal thickening. Despite failing to culture acid-fast bacilli from ascites, histological examination and culture of peritoneum revealed multidrug-resistant tuberculosis peritonitis. Peritoneal biopsy is mandatory when tuberculosis peritonitis is suspected.

DOI: 10.1002/ccr3.7759
PMCID: PMC10465719
PMID: 37655128

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

15. Time discrepancy for tuberculosis-negative microscopy and culture - the diagnostic gap remains: systematic analysis from a large tertiary care tuberculosis-clinic, Germany 2013-2017.

Int J Infect Dis. 2023 Sep;134:269-272. doi: 10.1016/j.ijid.2023.07.009. Epub 2023 Jul 16.

Kessel J(1), Göymen E(1), Wolf T(1), Wetzstein N(1), Küpper-Tetzel C(1), Behrens P(1), Borgans F(1), Balaban Ü(2), Hogardt M(3), Wichelhaus TA(3), Stephan C(4).

OBJECTIVES: Patients with open pulmonary tuberculosis (opTB) are subject to strict isolation rules. Sputum smear microscopy is used to determine infectivity, but sensitivity is lower than for culture. This study aimed to investigate the clinical relevance of this mismatch in contemporary settings.

METHODS: Differential results between microscopy and culture were determined at the time of microscopic sputum conversion, from all patients with opTB between 01/2013 and 12/2017. In addition, data on HIV, multi/extensive drug-resistant TB status, time to smear- and cultural-negativity conversion were analyzed; and a Kaplan-Meier curve was developed.

RESULTS: Of 118 patients with opTB, 58 had demographic data available for microbiological and clinical follow-up analysis; among these, 26 (44.8%) had still at least one positive culture result. Median time from opTB-treatment initiation to full microscopic sputum- or culture conversion, was 16.5 days (range 2-105), and 20 days (1-105), respectively (median difference: +3.5 days). Sixteen days after de-isolation, >90% had converted culturally. HIV- or multi/extensive drug-resistant TB status did not impact conversion time.

CONCLUSION: When patients with opTB were de-isolated after 3 negative sputum smear microscopy tests, a substantial part still revealed cultural growth of Mycobacterium tuberculosis complex, but it remains unclear, whether smear-negative and culturally-positive individuals on therapy are really infective. Thus, the clinical relevance of this finding warrants further investigation.

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PMID: 37454889 [Indexed for MEDLINE]

Conflict of interest statement: Declarations of Competing Interest Johanna Kessel and Nils Wetzstein declare no conflicts of interest; Michael Hogardt reports grants from Mukoviszidose Institut gGmbH and the German Federal Ministry

of Health, lecture honoraria from Landesärztekammer Hessen, bioMérieux and Pfizer, and funding from Merck AG. Thomas A. Wichelhaus reports research grants from MSD, Deutsche Krebshilfe, as well as speaker fees and consulting honoraria from Insmed, Osartis; Christoph Stephan received speaker fees/consulting/scientific conference sponsoring from AbbVie, ViiV, Gilead, MSD, Janssen, TAD. All received grants and financial support from all authors are declared outside the submitted work.

16. Mycobacterium tuberculosis carrying the rifampicin drug-resistance-conferring rpoB mutation H445Y is associated with suppressed immunity through type I interferons.

mBio. 2023 Sep 8:e0094623. doi: 10.1128/mbio.00946-23. Online ahead of print.

Bobba S(1), Howard NC(1), Das S(1), Ahmed M(1)(2), Tang L(3), Thirunavukkarasu S(1), Larsen MH(4), Mathema B(3), Divangahi M(5)(6)(7), Khader SA(1)(2).

Tuberculosis (TB) is one of the leading causes of death due to an infectious disease. The rise of multi-drug resistance (MDR) in Mycobacterium tuberculosis (Mtb), the causative agent of TB, presents a significant obstacle to TB control. While human studies report dysregulated immune responses during MDR TB, a clear understanding of the host-pathogen interactions of MDR Mtb is lacking. Here, we studied the immune responses induced by Mtb strains carrying two of the most common rifampicin drug-resistance (RDR)-conferring single-nucleotide polymorphisms (SNPs) in the RNA polymerase gene of Mtb, which accounts for nearly 90% of drug-resistance mutations found clinically in Mtb. During Mtb infection of primary human macrophages, we found that pro-inflammatory cytokine production was reduced upon infection with Mtb carrying the H445Y SNP but not the S450L SNP. Using a mouse model, we also characterized the host immune response in vivo following infection. Despite similar establishment of Mtb infection in the lung and dissemination to the peripheral organs, we show that infection with the RDR Mtb rpoB-H445Y strain, but not with the rpoB-S450L strain, resulted in a suppressed lung myeloid and lymphoid immune responses through type I IFN-dependent pathways, relative to wt Mtb. This suppressed host immunity had functional consequences in limiting control of RDR Mtb strains harboring rpoB-H445Y and led to worse pathology during chronic TB disease. Collectively, our results suggest that disease pathogenesis may be associated with specific RDR mutations in Mtb, which may differentially regulate immune responses. IMPORTANCE This study highlights the impact of specific rifampicin-resistance-conferring mutations on the host immune response to Mycobacterium tuberculosis (Mtb), the causative agent of tuberculosis (TB). Clinical reports have previously suggested that multi-drug-resistant) TB patients exhibit altered peripheral immune responses as compared with their

drug-sensitive TB counterparts. The murine model of infection with Mtb strains carrying drug-resistance-conferring mutations recapitulated these findings and allowed us to mechanistically interrogate the pathways responsible for driving the divergent immune responses. Our findings underscore the need for greater investigation into bacterial heterogeneity to better appreciate the diversity in host-pathogen interactions during TB disease.

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PMID: 37682004

17. Insight into the drug-resistant characteristics and genetic diversity of multidrug-resistant Mycobacterium tuberculosis in China.

Microbiol Spectr. 2023 Sep 21:e0132423. doi: 10.1128/spectrum.01324-23. Online ahead of print.

Song Z(#)(1)(2), Liu C(#)(2), He W(#)(1)(2), Pei S(#)(3), Liu D(1), Cao X(1)(2), Wang Y(1)(2), He P(1)(2), Zhao B(2), Ou X(2), Xia H(2), Wang S(2), Zhao Y(2).

Multidrug-resistant tuberculosis (MDR-TB) has a severe impact on public health. To investigate the drug-resistant profile, compensatory mutations and genetic variations among MDR-TB isolates, a total of 546 MDR-TB isolates from China underwent drug-susceptibility testing and whole genome sequencing for further analysis. The results showed that our isolates have a high rate of fluoroquinolone resistance (45.60%, 249/546) and a low proportion of conferring resistance to bedaquiline, clofazimine, linezolid, and delamanid. The majority of MDR-TB isolates (77.66%, 424/546) belong to Lineage 2.2.1, followed by Lineage 4.5 (6.41%, 35/546), and the Lineage 2 isolates have a strong association with pre-XDR/XDR-TB ($P < 0.05$) in our study. Epidemic success analysis using time-scaled haplotypic density (THD) showed that clustered isolates outperformed non-clustered isolates. Compensatory mutations happened in rpoA, rpoC, and non-RRDR of rpoB genes, which were found more frequently in clusters and were associated with the increase of THD index, suggesting that increased bacterial fitness was associated with MDR-TB transmission. In addition, the variants in resistance associated genes in MDR isolates are mainly focused on single nucleotide polymorphism mutations, and only a few genes have indel variants, such as katG, ethA. We also found some genes underwent indel variation correlated with the lineage and sub-lineage of isolates, suggesting the selective evolution of different lineage isolates. Thus, this analysis of the characterization and genetic diversity of MDR isolates would be helpful in developing effective strategies for treatment regimens and tailoring public interventions. IMPORTANCE Multidrug-resistant tuberculosis (MDR-TB) is a serious obstacle to tuberculosis prevention and control in China. This study provides

insight into the drug-resistant characteristics of MDR combined with phenotypic drug-susceptibility testing and whole genome sequencing. The compensatory mutations and epidemic success analysis were analyzed by time-scaled haplotypic density (THD) method, suggesting clustered isolates and compensatory mutations are associated with MDR-TB transmission. In addition, the insertion and deletion variants happened in some genes, which are associated with the lineage and sub-lineage of isolates, such as the mpt64 gene. This study offered a valuable reference and increased understanding of MDR-TB in China, which could be crucial for achieving the objective of precision medicine in the prevention and treatment of MDR-TB.

DOI: 10.1128/spectrum.01324-23
PMID: 37732780

18. Discovery of novel reversible inhibitor of DprE1 based on benzomorpholine for the treatment of tuberculosis.

Microbiol Spectr. 2023 Sep 12:e0472122. doi: 10.1128/spectrum.04721-22. Online ahead of print.

Xiang W(#)(1), He H(#)(1), Duan X(#)(1), He Z(2), Xu X(2), Liao M(3), Teng F(1), Li X(1), Luo T(1), Zeng J(2), Yu L(1), Gao C(4).

About a quarter of the world's population is infected with Mycobacterium tuberculosis, equivalent to about two billion people. With the emergence of multidrug-resistant tuberculosis, those existing anti-tuberculosis drugs no longer meet the demand for cure anymore; there is an urgent need for the development of new anti-tuberculosis drugs. Decaprenylphosphoryl-β-D-ribose 2´-epimerase (DprE1) has been proven to be a potential antimycobacterial target, and several inhibitors have entered clinical trial. Herein, we designed and synthesized a series of compounds based on the indole and benzomorpholine by using the strategy of scaffold hopping. The preferred compound B18 showed strong antimycobacterial activity in H37Rv and drug-resistant clinical isolates. In addition, compound B18 did not exhibit antimycobacterial efficacy against other species of strains. Subsequently, the target of B18 was identified as DprE1 by analyzing spontaneous compound-resistant mutation data, and a docking study was performed to illustrate the binding mode between B18 and DprE1. In general, compound B18 is compatible to current DprE1 inhibitors, even higher phosphodiesterase 6C selectivity and plasma protein binding rate, which represent a new type of effective reversible DprE1 inhibitor. IMPORTANCE Drug therapy remains the cornerstone of tuberculosis (TB) treatment, yet first-line anti-tuberculosis drugs are associated with significant adverse effects that can compromise patient outcomes. Moreover, prolonged and widespread use has led to

an alarming rise in drug-resistant strains of Mycobacterium tuberculosis, including multidrug-resistant [MDR-tuberculosis (TB)] and extensively drug-resistant (XDR-TB) forms. Urgent action is needed to develop novel anti-tuberculosis agents capable of overcoming these challenges. We report that compound B18, a decaprenylphosphoryl-β-D-ribose 2´-epimerase inhibitor with a benzomorpholine backbone, exhibits potent activity against not only the non-pathogenic strain H37Ra, but also the pathogenic strain H37Rv and clinical MDR and XDR strains. Preliminary druggability studies indicate that B18 possesses high safety and acceptable pharmacokinetic properties, rendering it a promising candidate for further development as a novel anti-tuberculosis agent.

DOI: 10.1128/spectrum.04721-22
PMID: 37698416

19. Radiomics analysis of lung CT for multidrug resistance prediction in active tuberculosis: a multicentre study.

Eur Radiol. 2023 Sep;33(9):6308-6317. doi: 10.1007/s00330-023-09589-x. Epub 2023 Apr 1.

Li Y(1), Xu Z(1), Lv X(1), Li C(1), He W(1), Lv Y(1), Hou D(2).

OBJECTIVES: Multidrug-resistant TB (MDR-TB) is a severe burden and public health threat worldwide. This study aimed to develop a radiomics model based on the tree-in-bud (TIB) sign and nodules and validate its predictive performance for MDR-TB.

METHODS: We retrospectively recruited 454 patients with proven active TB from two hospitals and classified them into three training and testing cohorts: TIB (n = 295, 102), nodules (n = 302, 97), and their combination (n = 261, 81). Radiomics features relating to TIB and nodules were separately extracted. The maximal information coefficient and recursive feature elimination were used to select informative features per the two signs. Two radiomics models were constructed to predict MDR-TB using a random forest classifier. Then, a combined model was built incorporating radiomics features based on these two signs. The capability of the models in the combined training and testing cohorts was validated with ROC curves.

RESULTS: Sixteen features were extracted from TIB and 15 from nodules. The AUCs of the combined model were slightly higher than those of the TIB model in the combined training cohort (0.911 versus 0.877, $p > 0.05$) and testing cohort (0.820 versus 0.786, $p < 0.05$) and similar to the performance of the nodules model in the combined training cohort (0.911 versus 0.933, $p > 0.05$) and testing

cohort (0.820 versus 0.855, $p > 0.05$).

CONCLUSIONS: The CT-based radiomics models hold promise for use as a non-invasive tool in the prediction of MDR-TB.
CLINICAL RELEVANCE STATEMENT: Our study revealed that complementary information regarding MDR-TB can be provided by radiomics based on the TIB sign and nodules. The proposed radiomics models may be new markers to predict MDR in active TB patients.

KEY POINTS: • This is the first study to build, validate, and apply radiomics based on tree-in-bud sign and nodules for the prediction of MDR-TB. • The radiomics model showed a favorable performance for the identification of MDR-TB. • The combined model holds potential to be used as a diagnostic tool in routine clinical practice.

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PMCID: PMC10067016
PMID: 37004571 [Indexed for MEDLINE]

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

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

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

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

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

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

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

21. The association of IL-17A rs2275913 single nucleotide polymorphism with anti-tuberculous drug resistance in patients with pulmonary tuberculosis.

J Genet Eng Biotechnol. 2023 Sep 4;21(1):90. doi: 10.1186/s43141-023-00542-5.

Elmadbouly AA(1), Abdul-Mohymen AM(2), Eltrawy HH(3), Elhasan HAA(4), Althoqapy AA(5), Amin DR(6).

BACKGROUND: Drug-resistant Tuberculosis (DR-TB) is a global health burden with high morbidity and mortality in developing countries including Egypt. The susceptibility to infection with DR-TB strains may be genetically determined. Several interleukin gene polymorphisms were investigated as risk factors for tuberculosis infection but focusing on their association with DR-TB was limited. Therefore, the objective of this study is to assess the association of IL 17 - 197 G > A (rs2275913) single nucleotide polymorphism (SNP) with susceptibility to DR-TB strains in comparison to drug-sensitive tuberculosis (DS-TB) strains in Egyptian patients with pulmonary TB. This cross-sectional study was conducted on 80 patients with DR-TB strains and 80 with DS-TB strains as a control group. Both age and sex were comparable among the study's groups. IL-17 - 197 G > A (rs2275913) SNP was genotyped by real-time PCR, and IL-17 serum concentration was measured by enzyme-linked immunosorbent assay (ELISA).

RESULTS: The GA and AA genotype frequencies of IL 17 - 197 G > A (rs2275913) SNP were significantly higher in patients with DR-TB strains than those with DS-TB strains ($p < 0.001$). The frequency of the A allele was significantly ($p < 0.001$)

higher in patients with DR-TB group (32.5%) compared to the control group (13.8%). Substantial higher serum levels of IL-17 were detected in the DR-TB group with significant association with AA and AG genotypes.

CONCLUSION: Polymorphism in IL-17 -197 G > A (rs2275913) resulted in higher serum levels of IL-17 and Egyptian patients with such polymorphism are three times at risk of infection with DR-TB strains than patients with wild type.

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PMCID: PMC10477154
PMID: 37665411

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

22. Mycobacterium tuberculosis complex whole-genome sequencing in New York State: Implementation of a reduced phenotypic drug susceptibility testing algorithm.

Tuberculosis (Edinb). 2023 Sep;142:102380. doi: 10.1016/j.tube.2023.102380. Epub 2023 Jul 22.

Shea J(1), Halse TA(2), Modestil H(3), Kearns C(4), Fowler RC(5), Da Costa-Carter CA(6), Siemetzki-Kapoor U(7), Leisner M(8), Lapierre P(9), Kohlerschmidt D(10), Rowlinson MC(11), Escuyer V(12), Musser KA(13).

Whole-genome sequencing (WGS) can predict drug resistance and antimicrobial susceptibility in Mycobacterium tuberculosis complex (MTBC) and has shown promise in partially replacing culture-based phenotypic drug susceptibility testing (pDST). We performed a two-year side by side study comparing the prediction of drug resistance and antimicrobial susceptibility by WGS molecular DST (mDST) to pDST to determine resistance at the critical concentration by Mycobacterial Growth Indicator Tube (MGIT) and agar proportion testing. Negative predictive values of WGS results were consistently high for the first-line drugs: rifampin (99.9%), isoniazid (99.0%), pyrazinamide (98.5%), and ethambutol (99.8%); the rates of resistance to these drugs, among strains in our population, are 2.9%, 10.4%, 46.3%, and 2.3%, respectively. WGS results were available an average 8 days earlier than first-line MGIT pDST. Based on these findings, we implemented a new testing algorithm with an updated WGS workflow in which strains predicted pan-susceptible were no longer tested by pDST. This algorithm was applied to 1177 isolates between October 2018 and September 2020, eliminating pDST for 66.6% of samples and reducing pDST for an additional 22.0%.

This algorithm change resulted in faster turnaround times and decreased cost while maintaining comprehensive antimicrobial susceptibility profiles of all culture-positive MTBC cases in New York.

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PMID: 37543009 [Indexed for MEDLINE]

23. The seroprevalence of anti-Histoplasma capsulatum IgG antibody among pulmonary tuberculosis patients in seven referral tuberculosis hospitals in Indonesia.

PLoS Negl Trop Dis. 2023 Sep 20;17(9):e0011575. doi: 10.1371/journal.pntd.0011575. eCollection 2023 Sep.

Kusmiati T(1), Burhan E(2), Sugiyono RI(3), Arlinda D(3), Naysilla AM(3), Wibisono BH(4), El Khair R(5), Candrawati NW(6), Sinaga BYM(7), Djaharrudin I(8), Lokida D(9), Kosasih H(3), Susanto NH(3), Butar Butar DP(3), Adawiyah R(10), Fatril AE(10), Karyana M(3), Denning DW(11), Wahyuningsih R(10)(12).

BACKGROUND: Histoplasma capsulatum exposure is rarely suspected in Indonesia. Pulmonary histoplasmosis can occur simultaneously with pulmonary tuberculosis (TB) or as an alternative diagnosis in clinically-diagnosed TB patients with no microbiological evidence of TB. This study aimed to determine the seroprevalence of anti-H. capsulatum IgG antibody among pulmonary TB patients.

METHODOLOGY: This was a sub-study of 306 participants from a prospective cohort pulmonary TB study conducted at seven TB referral hospitals in Indonesia. The study population was presumptive pulmonary TB adult patients who underwent microbiological TB examinations and were categorized as drug-sensitive (DS), drug-resistant (DR), and clinically-diagnosed TB. Anti-H. capsulatum IgG antibody levels at baseline were measured using MVista Histoplasma Ab enzyme immunoassays. Data were summarized using descriptive statistics. Bivariate and multivariate logistic regression analysis were performed to assess factors associated with anti-H. capsulatum IgG antibody positive result.

RESULTS: 12.7% (39/306) of pulmonary TB patients were positive for anti-H. capsulatum IgG antibodies (DR-TB patients (15.9%, 18/114), DS-TB (13.0%, 15/115), and clinically-diagnosed TB (7.8%, 6/77)). The median unit value of anti-H. capsulatum IgG antibody for all positive samples was 15.7 (IQR 10.2-28.9) EU. This median unit value was higher in clinically-diagnosed TB patients compared to DS-TB or DR-TB patients (38.1 (IQR 25.6-46.6) EU, 19.7 (IQR 12.3-28.9) EU, and 10.9 (IQR 9.2-15.4), respectively). There were 10 patients

(3.3%) with anti-H. capsulatum IgG antibody levels above 30 EU. Factors associated with the anti-H. capsulatum IgG antibody positive result were malignancies (OR 4.88, 95% CI 1.09-21.69, p = 0.037) and cavitary lesions (OR 2.27, 95% CI 1.09-4.70, p = 0.028).

CONCLUSIONS: Our results provide evidence of exposure to H. capsulatum among pulmonary TB patients in Indonesia. Further studies are needed to provide a comprehensive picture of this fungal disease in other populations and regions to enhance awareness among clinicians and public health officials.

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PMCID: PMC10511117
PMID: 37729126 [Indexed for MEDLINE]

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

24. Facilitators and barriers in implementation of active TB drug safety monitoring and management (aDSM) in programmatic management of drug resistance TB in Dar es Salaam region.

PLoS One. 2023 Sep 15;18(9):e0291225. doi: 10.1371/journal.pone.0291225. eCollection 2023.

Nyaulingo BC(1)(2), Mhimbira FA(1).

BACKGROUND: World Health Organization (WHO) recommends that active TB Dug Safety Monitoring and Management (aDSM) be adopted in countries' programmatic management of DR-TB services. In Tanzania, the National TB Leprosy Programme (NTLP), under the ministry of health, adopted the aDSM component in 2018. The study evaluated the facilitators and barriers of aDSM implementation in Dar es Salaam.

MATERIALS AND METHODS: This was a process evaluation study that adapted the descriptive cross-sectional approach, conducted in Dar es Salaam region. A total of 19 respondents, including clinicians, DOT (Direct Observed Therapy) nurses and key NTLP personnel, were interviewed using interview guides. Qualitative

content analysis based on Graneheim & Lundman was used to guide the analysis.

RESULTS: For aDSM to be implemented in a health facility, tools like forms for recoding and reporting, access to a functional laboratory for carrying out the required monitoring tests are a necessity. Moreover, the NTLP monitors the implementation through received aDSM reports and DR-TB supportive supervisions. However, it was found that in many health facilities, aDSM was partially being implemented due to various barriers: inadequate trained staff for aDSM implementation, administrative burden in reporting and delaying in AE management.

CONCLUSION: aDSM is inadequately being implemented due to the many setbacks faced by HCWs. aDSM-specific supportive supervisions and trainings to HCWs; incorporating the current manual aDSM reporting flow into the already existing electronic (Tanzania Medicine and Medical Drugs Authority) TMDA database seems useful.

DOI: 10.1371/journal.pone.0291225
PMCID: PMC10503757
PMID: 37713446 [Indexed for MEDLINE]

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

25. Nutritional support for adult patients with microbiologically confirmed pulmonary tuberculosis: outcomes in a programmatic cohort nested within the RATIONS trial in Jharkhand, India.

Lancet Glob Health. 2023 Sep;11(9):e1402-e1411. doi: 10.1016/S2214-109X(23)00324-8. Epub 2023 Aug 8.

Bhargava A(1), Bhargava M(2), Meher A(3), Teja GS(4), Velayutham B(3), Watson B(3), Benedetti A(5), Barik G(3), Singh VP(3), Singh D(3), Madhukeshwar AK(6), Prasad R(7), Pathak RR(8), Chadha V(9), Joshi R(10).

BACKGROUND: Undernutrition is a common comorbidity of tuberculosis in countries with a high tuberculosis burden, such as India. RATIONS is a field-based, cluster-randomised controlled trial evaluating the effect of providing

nutritional support to household contacts of adult patients with microbiologically confirmed pulmonary tuberculosis in Jharkhand, India, on tuberculosis incidence. The patient cohort in both groups of the trial was provided with nutritional support. In this study, we assessed the effects of nutritional support on tuberculosis mortality, treatment success, and other outcomes in the RATIONS patient cohort.

METHODS: We enrolled patients (aged 18 years or older) with microbiologically confirmed pulmonary tuberculosis across 28 tuberculosis units. Patients received nutritional support in the form of food rations (1200 kcal and 52 g of protein per day) and micronutrient pills. Nutritional support was for 6 months for drug-susceptible tuberculosis and 12 months for multidrug-resistant tuberculosis; patients with drug-susceptible tuberculosis could receive an extension of up to 6 months if their BMI was less than 18·5 kg/m2 at the end of treatment. We recorded BMI, diabetes status, and modified Eastern Cooperative Oncology Group (ECOG) performance status at baseline. Clinical outcomes (treatment success, tuberculosis mortality, loss to follow-up, and change in performance status) and weight gain were recorded at 6 months. We assessed the predictors of tuberculosis mortality with Poisson and Cox regression using adjusted incidence rate ratios (IRRs) and adjusted hazard ratios (HRs). The RATIONS trial is registered with the Clinical Trials Registry of India (CTRI/2019/08/020490).

FINDINGS: Between Aug 16, 2019, and Jan 31, 2021, 2800 patients (mean age 41·5 years [SD 14·5]; 1979 [70·7%] men and 821 [29·3%] women) were enrolled. At enrolment, 2291 (82·4%) patients were underweight (BMI <18·5 kg/m2), and 480 (17·3%) had a BMI of less than 14 kg/m2. The mean weight and BMI were 42·6 kg (SD 7·8) and 16·4 kg/m2 (2·6) in men and 36·1 kg (7·3) and 16·2 kg/m2 (2·9) in women. During the 6-month follow-up, treatment was successful in 2623 (93·7%) patients, 108 (3·9%) tuberculosis deaths occurred, 28 (1·0%) patients were lost to follow-up, and treatment failure was experienced by five (0·2%) patients. The median weight gain was 4·6 kg (IQR 2·8-6·8), but 1441 (54·8%) of 2630 patients remained underweight. At 2 months, 1444 (54·0%) of 2676 patients gained at least 5% of baseline weight. Baseline weight (adjusted IRR 0·95, 95% CI 0·90-0·99), BMI (0·88, 0·76-1·01), poor performance status (ECOG categories 3-4; 5·33, 2·90-9·79), diabetes (3·30, 1·65-6·72), and haemoglobin (0·85, 0·71-1·00) were predictors of tuberculosis mortality. A reduced hazard of death (adjusted HR 0·39, 95% CI 0·18-0·86) was associated with a 5% weight gain at 2 months.
I
NTERPRETATION: In this study, nutritional support was provided to a cohort with a high prevalence of severe undernutrition. Weight gain, particularly in the first 2 months, was associated with a substantially decreased hazard of tuberculosis mortality. Nutritional support needs to be an integral component of patient-centred care to improve treatment outcomes in such settings.

FUNDING: India Tuberculosis Research Consortium, Indian Council of Medical Research.

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PMID: 37567210 [Indexed for MEDLINE]

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

26. In vitro activity of new combinations of β-lactam and β-lactamase inhibitors against the Mycobacterium tuberculosis complex.

Microbiol Spectr. 2023 Sep 22:e0178123. doi: 10.1128/spectrum.01781-23. Online ahead of print.

Economou Lundeberg E(1), Andersson V(2), Wijkander M(3), Groenheit R(3), Mansjö M(3), Werngren J(3), Cortes T(4), Barilar I(5)(6), Niemann S(5)(6), Merker M(6)(7), Köser CU(8), Davies Forsman L(2)(9).

As meropenem-clavulanic acid is recommended for the treatment of drug-resistant tuberculosis, the repurposing of new carbapenem combinations may provide new treatment options, including oral alternatives. Therefore, we studied the in vitro activities of meropenem-vaborbactam, meropenem-clavulanic acid, and tebipenem-clavulanic acid. One hundred nine Mycobacterium tuberculosis complex (MTBC) clinical isolates were tested, of which 69 were pan-susceptible and the remaining pyrazinamide- or multidrug-resistant. Broth microdilution MICs were determined using the EUCAST reference method. Meropenem and tebipenem were tested individually and in combination with vaborbactam 8 mg/L and clavulanic-acid 2 and 4 mg/L, respectively. Whole-genome sequencing was performed to explore resistance mechanisms. Clavulanic acid lowered the modal tebipenem MIC approximately 16-fold (from 16 to 1 mg/L). The modal meropenem MIC was reduced twofold by vaborbactam compared with an approximately eightfold decrease by clavulanic acid. The only previously described high-confidence carbapenem resistance mutation, crfA T62A, was shared by a subgroup of lineage 4.3.4.1 isolates and did not correlate with elevated MICs. The presence of a β-lactamase inhibitor reduced the MTBC MICs of tebipenem and meropenem. The resulting MIC distribution was lowest for the orally available drugs tebipenem-clavulanic acid. Whether this in vitro activity translates to similar

or greater clinical efficacy of tebipenem-clavulanic acid compared with the currently WHO-endorsed meropenem-clavulanic acid requires clinical studies. IMPORTANCE Repurposing of already approved antibiotics, such as β-lactams in combination with β-lactamase inhibitors, may provide new treatment alternatives for drug-resistant tuberculosis. Meropenem-clavulanic acid was more active in vitro compared to meropenem-vaborbactam. Notably, tebipenem-clavulanic acid showed even better activity, raising the potential of an all-oral treatment option. Clinical data are needed to investigate whether the better in vitro activity of tebipenem-clavulanic acid correlates with greater clinical efficacy compared with the currently WHO-endorsed meropenem-clavulanic acid.

DOI: 10.1128/spectrum.01781-23
PMID: 37737628

27. Synthesis and Structure-Activity Relationships of a New Class of Oxadiazoles Targeting DprE1 as Antitubercular Agents.

ACS Med Chem Lett. 2023 Aug 15;14(9):1275-1283. doi: 10.1021/acsmedchemlett.3c00295. eCollection 2023 Sep 14.

Yadav VD(1), Boshoff HI(1), Trifonov L(1), Roma JSO(1), Ioerger TR(2), Barry CE 3rd(1), Oh S(1).

The continuing prevalence of drug-resistant tuberculosis threatens global TB control programs, highlighting the need to discover new drug candidates to feed the drug development pipeline. In this study, we describe a high-throughput screening hit (4-benzylpiperidin-1-yl)(1-(5-phenyl-1,3,4-oxadiazol-2-yl)piperidin-4-yl)methanone (P1) as a potent antitubercular agent. Structure-activity guided synthesis led to the discovery of several analogs with high in vitro potency. P1 was found to have promising potency against many drug-resistant strains, as well as drug-susceptible clinical isolates. It also showed cidality against Mtb growing in host macrophages. Whole genome sequencing of genomic DNA from resistant mutants raised to P1 revealed mutations in decaprenylphosphoryl-β-d-ribose 2'-oxidase (DprE1). This novel oxadiazole scaffold expands the set of chemical tools for targeting a well-validated pathway to treat tuberculosis.

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

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28. [Management of drug-resistant tuberculosis].

Dtsch Med Wochenschr. 2023 Sep;148(19):1236-1241. doi: 10.1055/a-1939-0000. Epub 2023 Sep 15.

[Article in German]

Lange C.

The spread of multidrug-resistant Mycobacterium tuberculosis bacteria jeopardizes tuberculosis control, especially in the WHO Europe region. Following the availability of novel drugs and treatment regimens the World Health Organization has updated management recommendations for patients affected by drug-resistant tuberculosis. These novel recommendations include a significant reduction in the duration of therapy. This review presents the epidemiology and diagnostics of antibiotic-resistant tuberculosis as well as up-to-date treatment recommendations.

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PMID: 37714164 [Indexed for MEDLINE]

Conflict of interest statement: Finanzielle Förderung: Die Entstehung dieser Arbeit wurde vom Deutschen Zentrum für Infektionsforschung (DZIF) (Fördermaßnahme 02.709 ClinTB; C.L.) gefördert. C.L. gibt an Honorare für Vorträge auf Symposien erhalten zu haben, die von den Firmen Insmed, Gilead und GSK finanziell unterstützt wurden. Er hat Honorare für wissenschaftliche Beratungen der Firma Insmed erhalten. Er ist wissenschaftlicher Berater von Ärzte ohne Grenzen (MSF) für Arzneimittelstudien der Tuberkulose.

29. Rifampicin drug resistance and host immunity in tuberculosis: more than meets the eye.

Trends Immunol. 2023 Sep;44(9):712-723. doi: 10.1016/j.it.2023.07.003. Epub 2023 Aug 3.

Bobba S(1), Khader SA(2).

Tuberculosis (TB) is the leading cause of death due to an infectious agent, with more than 1.5 million deaths attributed to TB annually worldwide. The global dissemination of drug resistance across Mycobacterium tuberculosis (Mtb) strains, causative of TB, resulted in an estimated 450 000 cases of drug-resistant (DR) TB in 2021. Dysregulated immune responses have been observed in patients with multidrug resistant (MDR) TB, but the effects of drug resistance acquisition and impact on host immunity remain obscure. In this review, we compile studies that span aspects of altered host-pathogen interactions and highlight research that explores how drug resistance and immunity might intersect. Understanding the immune processes differentially induced during DR TB would aid the development of rational therapeutics and vaccines for patients with MDR TB.

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PMID: 37543504 [Indexed for MEDLINE]

Conflict of interest statement: Declaration of interests None declared by authors.

30. Effectiveness and safety of tuberculosis preventive treatment for contacts of multidrug-resistant tuberculosis patients: A systematic review and Meta-analysis.

Clin Microbiol Infect. 2023 Sep 21:S1198-743X(23)00477-9. doi: 10.1016/j.cmi.2023.09.015. Online ahead of print.

Zhou G(1), Luo S(2), He J(3), Chen N(4), Zhang Y(4), Cai S(5), Guo X(5), Chen H(6), Song C(7).

BACKGROUND: Contacts of patients with multidrug-resistant tuberculosis (MDR-TB) are at risk of developing TB disease. Tuberculosis preventive treatment (TPT) is an intervention that can potentially reduce this risk.

OBJECTIVES: To evaluate the effectiveness and safety of TPT for contacts of MDR-TB patients.

DATA SOURCES: EMBASE, PubMed, Web of Science, and the Cochrane Library were searched for eligible studies on July 24, 2023, without start date restrictions.

STUDY ELIGIBILITY CRITERIA: We included studies that compared TPT with no treatment in contacts of MDR-TB patients and reported outcomes of progression to TB disease.

PARTICIPANTS: Contacts of MDR-TB patients.

INTERVENTIONS: TPT.

ASSESSMENT OF RISK OF BIAS: A modified version of the Newcastle-Ottawa Scale was used.

METHODS OF DATA SYNTHESIS: Random-effects meta-analysis was utilized to calculate the relative risk (RR) for disease progression to TB in contacts of MDR-TB patients who received TPT compared to those who did not. Additionally, completion, adverse effect, and discontinued rates were assessed.

RESULTS: Involving 1105 individuals from eleven studies, the pooled RR for disease progression in contacts receiving TPT versus those without treatment was 0.34 (95% CI: 0.16-0.72). Subgroup analysis indicated a lower pooled RR for regimens based on the drug-resistance profile of the index TB patients compared to uniform treatment regimens (0.22 [95% CI: 0.06-0.84] vs. 0.49 [95% CI: 0.17-1.35]), although not statistically significant. The pooled completed rate was 83.8%, adverse effect rate was 22.9%, and discontinued rate was 6.5%. After excluding the levofloxacin and pyrazinamide regimen study, the completed rate increased to 88.0%, and adverse effects and discontinued rates decreased to 8.0% and 4.0%, respectively.

DISCUSSION: TPT reduces TB disease progression risk in contacts of MDR-TB patients. Tailored TPT regimens based on drug-resistance profiles may offer additional benefits. Furthermore, efforts to improve completed rates and manage adverse effects are essential for optimizing effectiveness and safety.

DOI: 10.1016/j.cmi.2023.09.015
PMID: 37741621

31. Questioning bedaquiline availability.

Lancet Infect Dis. 2023 Sep;23(9):e338. doi: 10.1016/S1473-3099(23)00496-6. Epub 2023 Jul 31.

Holt E.

DOI: 10.1016/S1473-3099(23)00496-6
PMID: 37536359 [Indexed for MEDLINE]

32. Intricate link between siderophore secretion and drug efflux in Mycobacterium

tuberculosis.

Antimicrob Agents Chemother. 2023 Sep 7:e0162922. doi: 10.1128/aac.01629-22. Online ahead of print.

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

Drug-resistant Mycobacterium tuberculosis is a worldwide health-care problem rendering current tuberculosis (TB) drugs ineffective. Drug efflux is an important mechanism in bacterial drug resistance. The MmpL4 and MmpL5 transporters form functionally redundant complexes with their associated MmpS4 and MmpS5 proteins and constitute the inner membrane components of an essential siderophore secretion system of M. tuberculosis. Inactivating siderophore secretion is toxic for M. tuberculosis due to self-poisoning at low-iron conditions and leads to a strong virulence defect in mice. In this study, we show that M. tuberculosis mutants lacking components of the MmpS4-MmpL4 and MmpS5-MmpL5 systems are more susceptible to bedaquiline, clofazimine, and rifabutin, important drugs for treatment of drug-resistant TB. While genetic deletion experiments revealed similar functions of the MmpL4 and MmpL5 transporters in siderophore and drug secretion, complementation experiments indicated that the MmpS4-MmpL4 proteins alone are not sufficient to restore drug efflux in an M. tuberculosis mutant lacking both operons, in contrast to MmpS5-MmpL5. Importantly, an M. tuberculosis mutant lacking the recently discovered periplasmic Rv0455c protein, which is also essential for siderophore secretion, is more susceptible to the same drugs. These results reveal a promising target for the development of dual-function TB drugs, which might poison M. tuberculosis by blocking siderophore secretion and synergize with other drugs by impairing drug efflux.

DOI: 10.1128/aac.01629-22
PMID: 37676015

33. Pediatric multi-drug-resistant tuberculosis in Germany - diagnostic and therapeutic challenges of an "orphan disease".

Eur J Pediatr. 2023 Sep 14. doi: 10.1007/s00431-023-05167-x. Online ahead of print.

Schäfer HL(1), Barker M(2), Follmann P(3), Günther A(2), Hörning A(4), Kaiser-Labusch P(5), Kerzel S(6), Maier C(7), Roth S(6), Schmidt C(8), Schütz K(9), Stehling F(10), Struffert M(7), Timmesfeld N(11), Vöhringer P(12), Brinkmann F(7)(13).

Delay in diagnosing multidrug-resistant tuberculosis (MDR-pTB) in children

prolongs time to effective treatment. Data on risk factors for pediatric MDR from low-incidence countries are scarce. Retrospective nationwide case-control study to analyze MDR-pTB cases in Germany between 2010 and 2020 in comparison to a drug-susceptible (DS)-pTB group. We included 52 MDR cases (24 tuberculosis (TB), 28 TB infection (TBI); mean age 7.3 years) and 56 DS cases (31 TB, 26 TBI; mean age 7.9 years). Groups were similar for sex, household size, and migration background. Compared to the DS group, more children with MDR were born in the Commonwealth of Independent States (CIS) (22% MDR-pTB vs. 13% DS-pTB, n.s.) and had more MDR index cases (94% MDR-pTB, 5% DS-pTB, $p < 0.001$). The interval between first healthcare contact and initiation of effective therapy was significantly longer in MDR-pTB (47 days) than in DS-pTB (11 days, $p < 0.001$), correlating with disease progression. Treatment for MDR-pTB was successful in 74%, but 22% experienced long-term adverse effects (e.g., hepatopathy, hearing loss).
CONCLUSIONS: Close contact to MDR cases or birth in MDR-TB-high-incidence countries are risk factors for MDR-pTB. Early identification of potential MDR index cases by contact investigation, and susceptibility testing in children from high-burden MDR-TB countries are essential for timely diagnosis and treatment, reducing the severity of disease and treatment side effects.
TRIAL REGISTRATION: Deutsches Register Klinischer Studien (https://www.drks.de/drks_web/navigate.do?navigationId=trial.HTML&TRIAL_ID=DRKS00023817), DRKS00023817, 2020-09-08.
WHAT IS KNOWN: •Management of children with MDR-TB remains challenging due to difficulties in diagnosing MDR-TB (lack of information on MDR index case, lack of microbiological confirmation in paucibacillary disease). •Choice of treatment regimen and monitoring of side effects.
WHAT IS NEW: •Children with an MDR-TB index or born in a MDR-TB-high-incidence country are at higher risk of developing MDR-TB in a low incidence country. •The time lag to initiate treatment in MDR-TB is longer than in DS-TB and MDR-TB treatment involves a higher risk of adverse effects in longer treatment regimens especially with injectables.

DOI: 10.1007/s00431-023-05167-x
PMID: 37707590

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

Immunology. 2023 Sep 16. doi: 10.1111/imm.13698. Online ahead of print.

Imperiale BR(1), Gamberale A(2), Yokobori N(3), García A(2), Bartoletti B(2),

Aidar O(2), López B(3), Cruz V(2), González Montaner P(2)(4), Palmero DJ(2)(4), de la Barrera S(1).

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

DOI: 10.1111/imm.13698
PMID: 37715690

35. Antitubercular drugs: possible role of natural products acting as antituberculosis medication in overcoming drug resistance and drug-induced hepatotoxicity.

Naunyn Schmiedebergs Arch Pharmacol. 2023 Sep 4. doi: 10.1007/s00210-023-02679-z. Online ahead of print.

Rana HK(1)(2), Singh AK(1)(3), Kumar R(1)(4), Pandey AK(5).

Mycobacterium tuberculosis (Mtb) is a pathogenic bacterium which causes tuberculosis (TB). TB control programmes are facing threats from drug resistance. Multidrug-resistant (MDR) and extensively drug-resistant (XDR) Mtb

strains need longer and more expensive treatment with many medications resulting in more adverse effects and decreased chances of treatment outcomes. The World Health Organization (WHO) has emphasised the development of not just new individual anti-TB drugs, but also novel medication regimens as an alternative treatment option for the drug-resistant Mtb strains. Many plants, as well as marine creatures (sponge; Haliclona sp.) and fungi, have been continuously used to treat TB in various traditional treatment systems around the world, providing an almost limitless supply of active components. Natural products, in addition to their anti-mycobacterial action, can be used as adjuvant therapy to increase the efficacy of conventional anti-mycobacterial medications, reduce their side effects, and reverse MDR Mtb strain due to Mycobacterium's genetic flexibility and environmental adaptation. Several natural compounds such as quercetin, ursolic acid, berberine, thymoquinone, curcumin, phloretin, and propolis have shown potential anti-mycobacterial efficacy and are still being explored in preclinical and clinical investigations for confirmation of their efficacy and safety as anti-TB medication. However, more high-level randomized clinical trials are desperately required. The current review provides an overview of drug-resistant TB along with the latest anti-TB medications, drug-induced hepatotoxicity and oxidative stress. Further, the role and mechanisms of action of first and second-line anti-TB drugs and new drugs have been highlighted. Finally, the role of natural compounds as anti-TB medication and hepatoprotectants have been described and their mechanisms discussed.

DOI: 10.1007/s00210-023-02679-z
PMID: 37665346

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

Eur J Clin Microbiol Infect Dis. 2023 Sep 23. doi: 10.1007/s10096-023-04663-0. Online ahead of print.

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

Tuberculosis, caused by Mycobacterium tuberculosis, is a fatal infectious disease that prevails to be the second leading cause of death from a single infectious agent despite the availability of multiple drugs for treatment. The current treatment regimen involves the combination of several drugs for 6 months that remain ineffective in completely eradicating the infection because of several drawbacks, such as the long duration of treatment and the side effects of drugs causing non-adherence of patients to the treatment regimen. Autophagy

is an intracellular degradative process that eliminates pathogens at the early stages of infection. Mycobacterium tuberculosis's unique autophagy-blocking capability makes it challenging to eliminate compared to usual pathogens. The present review discusses recent advances in autophagy-inhibiting factors and mechanisms that could be exploited to identify autophagy-inducing chemotherapeutics that could be used as adjunctive therapy with the existing first-line anti-TB agent to shorten the duration of therapy and enhance cure rates from multidrug-resistant tuberculosis (MDR-TB) and extreme drug-resistant tuberculosis (XDR-TB).

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

37. 1-Year Incidence of Tuberculosis Infection and Disease Among Household Contacts of Rifampin- and Multidrug-Resistant Tuberculosis.

Clin Infect Dis. 2023 Sep 18;77(6):892-900. doi: 10.1093/cid/ciad301.

Krishnan S(1), Wu X(2), Kim S(3), McIntire K(1), Naini L(4), Hughes MD(2), Dawson R(5), Mave V(1)(6), Gaikwad S(6), Sanchez J(7), Mendoza-Ticona A(8), Gonzales P(9), Comins K(8), Shenje J(10), Fontain SN(11), Omozoarhe A(12), Mohapi L(13), Lalloo UG(14), Garcia Ferreira AC(15), Mugah C(16), Harrington M(17), Shah NS(18), Hesseling AC(19), Churchyard G(20)(21)(22), Swindells S(23), Gupta A(1)(6); AIDS Clinical Trials Group A5300/International Maternal Pediatric Adolescent AIDS Clinical Trials I2003 Protecting Households on Exposure to Newly Diagnosed Index Multidrug-resistant Tuberculosis Patients Feasibility Study Team* (Additional study group members are listed in the Acknowledgment section).

BACKGROUND: Tuberculosis infection (TBI) and TB disease (TBD) incidence remains poorly described following household contact (HHC) rifampin-/multidrug-resistant TB exposure. We sought to characterize TBI and TBD incidence at 1 year in HHCs and to evaluate TB preventive treatment (TPT) use in high-risk groups.

METHODS: We previously conducted a cross-sectional study of HHCs with rifampin-/multidrug-resistant TB in 8 high-burden countries and reassessed TBI (interferon-gamma release assay, HHCs aged ≥5 years) and TBD (HHCs all ages) at 1 year. Incidence was estimated across age and risk groups (<5 years; ≥5 years, diagnosed with human immunodeficiency virus [HIV]; ≥5 years, not diagnosed with HIV/unknown, baseline TBI-positive) by logistic or log-binomial regression fitted using generalized estimating equations.

RESULTS: Of 1016 HHCs, 850 (83.7%) from 247 households were assessed (median, 51.4 weeks). Among 242 HHCs, 52 tested interferon-gamma release assay-positive, yielding a 1-year 21.6% (95% confidence interval [CI], 16.7-27.4) TBI cumulative incidence. Sixteen of 742 HHCs developed confirmed (n = 5), probable (n = 3), or possible (n = 8) TBD, yielding a 2.3% (95% CI, 1.4-3.8) 1-year cumulative incidence (1.1%; 95% CI, .5-2.2 for confirmed/probable TBD). TBD relative risk was 11.5-fold (95% CI, 1.7-78.7), 10.4-fold (95% CI, 2.4-45.6), and 2.9-fold (95% CI, .5-17.8) higher in age <5 years, diagnosed with HIV, and baseline TBI high-risk groups, respectively, vs the not high-risk group (P = .0015). By 1 year, 4% (21 of 553) of high-risk HHCs had received TPT.

CONCLUSIONS: TBI and TBD incidence continued through 1 year in rifampin-/multidrug-resistant TB HHCs. Low TPT coverage emphasizes the need for evidence-based prevention and scale-up, particularly among high-risk groups.

DOI: 10.1093/cid/ciad301
PMID: 37227925 [Indexed for MEDLINE]

Conflict of interest statement: Potential conflicts of interest . S. G. and V. M. report grant UM1AI069465 provided by NIAID. S. S. reports research grants from ViiV Healthcare (paid to institution) and unpaid participation as chair of an NIH, NIAID data and safety monitoring board (DSMB). S. Ki. reports grants from NIH (CRDF Global) and unpaid participation on the DRAMATIC Study DSMB. S. Kr. reports receipt of grants CRDF and RePORT India phase II, payment or honoraria from Clinical Care Options, LLC, and travel support from CROI 2022 New Investigator Scholarship. M. D. H. reports NIH research and training grants; travel support from CROI (paid to author); unpaid participation on a Medicins Sans Frontiers DSMB; and a role as board member for the Botswana Harvard Partnership via employer. A. G. reports grants or contracts from NIH, UNITAID, and the Centers for Disease Control and Prevention; travel support from CROI 2023 (paid to author); participation on the NIH/NAID Advisory Council and Indo US Science Technology Governing Board; and roles on the IMPAACT Network TB Scientific Committee and World Health Organization MDR TB Guidelines Committee. U. G. L. reports an ACTG NIH grant to a clinical research site. L. M. reports receipt of clinical trial fees to their institution from Merck Sharp & Dohme Corp, Adagio Therapeutics, Inc, ViiV Healthcare, and Johnson & Johnson. A. C. H. reports grant funding from DAIDS, NIAID, and NIH as one of the protocol chairs. G. C. reports a grant from DAID (paid to their institution). 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. Clofazimine: A journey of a drug.

Biomed Pharmacother. 2023 Sep 22;167:115539. doi: 10.1016/j.biopha.2023.115539. Online ahead of print.

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

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

DOI: 10.1016/j.biopha.2023.115539
PMID: 37742606

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

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

Spine Deform. 2023 Sep 8. doi: 10.1007/s43390-023-00764-0. Online ahead of print.

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

PURPOSE: This study aimed to investigate the impact of vertebral column destruction and kyphotic deformity due to spinal tuberculosis on pulmonary functions in paediatric patients.

METHODS: A cross-sectional study was conducted, involving 30 patients diagnosed with healed spinal tuberculosis, aged 7-18 years. Detailed radiographic measurements, including the level of involvement, kyphosis angle, Spinal Deformity Index (SDI), and drug-resistance status, were compared with various pulmonary function parameters.

RESULTS: The mean age of the study group was 12.8 ± 2.7 years (range 7-17 years), consisting of 11 males and 19 females. Fourteen patients were managed conservatively and 16 were managed operatively. The mean SDI was 5.2 ± 4.7. The mean kyphotic angle was 31.3° ± 25.3. The average number of involved vertebrae was 2.6 ± 1.5. Pulmonary functions were classified as restrictive in 24 patients, normal in 4 patients, obstructive in 1 patient, and mixed in 1 patient. Multidrug-resistant tuberculosis (MDR-TB) was detected in 5 (16.7%) patients, while the remaining 25 (83.3%) patients were sensitive to conventional antitubercular drugs. The correlation coefficients between the percentage reduction in forced vital capacity (FVC) and kyphosis angle, SDI, and number of vertebrae were 0.4 ($p = 0.026$), 0.4 ($p = 0.028$), and 0.19 ($p = 0.295$), respectively. The mean percentage reduction in FVC and total lung capacity (TLC) were 35.8 ± 15.7 and 6.2 ± 2.3, respectively. No significant association was observed between pulmonary functions and drug sensitivity status ($p = 0.074$).

CONCLUSIONS: Paediatric spinal tuberculosis can lead to thoracic insufficiency due to progressive destruction and shortening of the spinal column, spinal growth inhibition, and kyphotic deformity. Management of these cases should focus on promoting normal lung development while ensuring disease resolution and deformity correction. Further research should explore growth conserving or growth guiding systems to address or prevent growth retardation and simultaneously provide spinal stabilization.

DOI: 10.1007/s43390-023-00764-0
PMID: 37682414

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

J Chemother. 2023 Sep;35(5):404-410. doi: 10.1080/1120009X.2022.2136447. Epub 2022 Nov 2.

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 [Indexed for MEDLINE]

41. Tuberculosis contact-tracing results in childhood: a retrospective study in a tertiary-care children's hospital in Turkey.

Paediatr Int Child Health. 2023 Sep 6:1-8. doi: 10.1080/20469047.2023.2252167. Online ahead of print.

Yaşar Durmuş S(1), Tanır G(2), Aydın Teke T(2), Kaman A(2), Yalçınkaya R(2), Üner Ç(3), Öz FN(2).

BACKGROUND: Smear-positive adults with tuberculosis are the main source of

childhood tuberculosis. The evaluation of children exposed to tuberculosis and determination of the disease stages are the cornerstones of managing childhood tuberculosis.

AIM: To determine the frequency of tuberculous contact, latent tuberculosis infection and tuberculosis disease in children who were in contact with smear-positive adults.

METHODS: This is a single-centre, retrospective study. The medical records of children exposed to tuberculosis (<18 years old) between 2014 and 2018 were investigated. After diagnosing the index cases, the children were referred to the hospital. To identify the children in contact with adults with tuberculosis, a careful medical history, demographic features and physical examination, tuberculin skin test, postero-anterior and lateral chest radiographs, and, if necessary, chest computed tomography and microbiological tests were undertaken. The children's final diagnosis, treatment regimens and follow-up were documented. The sensitivity, specificity and positive and negative predictive values, tuberculin skin test and chest radiograph imaging were assessed and compared with computed tomography results.

RESULTS: A total of 150 paediatric patients were exposed to 88 index cases. These were fathers in 29.3% of cases and mothers in 10% of cases. Of the children, 131 (87.3%) were asymptomatic, and physical examination was normal in all children, apart from one who had respiratory symptoms. The tuberculin skin test results were positive in 60 (43%) patients and chest radiograph was abnormal in 100 (66%) children. Findings were consistent with tuberculosis in 34 (40%) of the 84 patients who underwent computed tomography. Fifty (38.5%) of the remaining children were defined as having been in contact with a case of tuberculosis, 41 (31.5%) had latent tuberculous infection and 39 (30%) had tuberculosis disease.

CONCLUSION: Pulmonary tuberculosis is asymptomatic in most children but with meticulous use of computed tomography it can be detected in asymptomatic children who have had close contact with tuberculosis.Abbreviation: AFB: acid-fast bacilli; AUC: area under the curve; BCG: bacillus Calmette-Guérin; CI: confidence interval; CT: computed tomography; CXR: chest radiograph; HIV: human immunodeficiency virus; ICD-10: International Classification of Diseases 10; LTBI: latent tuberculosis infection; MDR-TB: multi-drug-resistant tuberculosis; NPV: negative predictive value; PCR: polymerase chain reaction; PPV: positive predictive value; ROC: receiver operating characteristics; SD: standard deviation; TB: tuberculosis; TST: tuberculin skin test; XDR-TB: extensively drug-resistant tuberculosis.

DOI: 10.1080/20469047.2023.2252167

PMID: 37671805

42. Clinical Utility of Contezolid-Containing Regimens in 25 Cases of Linezolid-Intolerable Tuberculosis Patients.

Infect Drug Resist. 2023 Sep 19;16:6237-6245. doi: 10.2147/IDR.S425743. eCollection 2023.

Wang J(1), Nie W(1), Ma L(1), Li Q(1), Geng R(2), Shi W(1), Chu N(1).

OBJECTIVE: Linezolid is increasingly used in the treatment of multidrug-resistant (MDR) M. tuberculosis (TB) with good efficacy; however, its clinical use is limited by intolerable adverse events (AEs). This usually results in dose adjustment or even discontinuation. Contezolid is a new oxazolidinone antibiotic with in vitro antibacterial activity against MDR TB equivalent to linezolid, but its safety and efficacy in MDB TB treatment has not been established.

METHODS: We conducted a retrospective study on 25 TB patients who received both linezolid and contezolid in Beijing Chest Hospital from January 1, 2022, to January 31, 2023. All patients received linezolid-containing anti-TB regimen first and then switched to contezolid-containing regimens due to the intolerable linezolid-related AEs.

RESULTS: Most (68%, 17/25) of the patients were diagnosed with RR-TB or MDR-TB. A total of 30 AEs were reported in these patients. About 26.7% (8/30) of the AEs were Grade 3 (severe) in severity. After switching to contezolid-containing anti-TB regimens for at least 1 month, the linezolid-related AEs were resolved or improved in 90% of the cases. Clinical improvement was observed in all patients after treatment with contezolid-containing regimen, with negative results of sputum culture and/or smear for M. tuberculosis in 84% of the patients.

CONCLUSION: Contezolid can be the first choice instead of linezolid to combine with other anti-TB drugs if necessary. Well-designed clinical trials are required to further confirm the safety and efficacy of contezolid in the treatment of TB patients.

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Conflict of interest statement: All authors declare that they have no conflicts of interest in this work.

43. Determining the diagnostic potential of Truenat MTB Plus for Tubercular lymphadenitis and detection of drug resistance and a comparison with GeneXpert Ultra.

Tuberculosis (Edinb). 2023 Sep;142:102379. doi: 10.1016/j.tube.2023.102379. Epub 2023 Jul 17.

Sharma K(1), Sharma M(2), Gupta N(3), Modi T(4), Joshi H(1), Shree R(5), Sharma A(6).

SETTING: Tubercular lymphadenitis (TBLA), the most common form of extrapulmonary tuberculosis, is a diagnostic challenge.
OBJECTIVE: Truenat MTB Plus (TruPlus) along with Truenat Rif assay (TruRif) was evaluated for detection of TBLA and rifampicin resistance and compared with GeneXpert Ultra (Xpert Ultra).
DESIGN: 100 fine-needle aspirated specimens [50 confirmed by culture/smear/cytology, 20 clinically suspected, and 30 controls], processed in the mycobacteriology division of department of microbiology were subjected to TruPlus and TruRif, Xpert Ultra and multiplex PCR. The results of TBLA detection were compared against composite reference standard (CRS) and those of rifampicin resistance were compared against phenotypic drug susceptibility testing and rpoB gene sequencing.
RESULTS: In comparison to CRS, the diagnostic yield of TruPlus, Xpert Ultra and MPCR was 77.14%, 59.18% and 84.28%, respectively; with substantial agreement for TruPlus (k = 0.66) and MPCR (k = 0.76) and moderate for Xpert Ultra (k = 0.60). TruRif reported four cases as RifR and Xpert Ultra reported two. On comparing with phenotypic DST and gene sequencing, only two cases of RifR were confirmed, hence TruRif reported false-RifR in two cases.
CONCLUSION: TruPlus could be used as a reliable tool for diagnosing TBLA. The reporting of RifR by TruRif should be confirmed by phenotypic DST or gene sequencing.

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Conflict of interest statement: Declaration of competing interest None.

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

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

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45. Arylidene and amino spacer-linked rhodanine-quinoline hybrids as upgraded antimicrobial agents.

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Antibiotic resistance associated with various microorganisms such as Gram-positive, Gram-negative, fungal strains, and multidrug-resistant tuberculosis increases the risk of healthcare survival. Preliminary therapeutics becoming ineffective that might lead to noteworthy mortality presents a crucial challenge for the scientific community. Hence, there is an urgent need to

develop hybrid compounds as antimicrobial agents by combining two or more bioactive heterocyclic moieties into a single molecular framework with fewer side effects and a unique mode of action. This review highlights the recent advances (2013-2023) in the pharmacology of rhodanine-linked quinoline hybrids as more effective antimicrobial agents. In the drug development process, linker hybrids acquire the top position due to their excellent π-stacking and Van der Waals interaction with the DNA active sites of pathogens. A molecular hybridization strategy has been optimized, indicating that combining these two bioactive moieties with an arylidene and an amino spacer linker increases the antimicrobial potential and reduces drug resistance. Moreover, the structure-activity relationship study is discussed to express the role of various functional groups in improving and decrementing antimicrobial activities for rational drug design. Also, a linker approach may accelerate the development of dynamic antimicrobial agents through molecular hybridization.

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PMID: 37697906

46. Investigation of genomic mutations and their association with phenotypic resistance to new and repurposed drugs in Mycobacterium tuberculosis complex clinical isolates.

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BACKGROUND: WGS has the potential to detect resistance-associated mutations and guide treatment of MDR TB. However, the knowledge base to confidently interpret mutations associated with the new and repurposed drugs is sparse, and phenotypic drug susceptibility testing is required to detect resistance.

METHODS: We screened 900 Mycobacterium tuberculosis complex genomes from Ireland, a low TB incidence country, for mutations in 13 candidate genes and assessed their association with phenotypic resistance to bedaquiline, clofazimine, linezolid, delamanid and pretomanid.

RESULTS: We identified a large diversity of mutations in the candidate genes of 195 clinical isolates, with very few isolates associated with phenotypic resistance to bedaquiline (n = 4), delamanid (n = 4) and pretomanid (n = 2). We identified bedaquiline resistance among two drug-susceptible TB isolates that

harboured mutations in Rv0678. Bedaquiline resistance was also identified in two MDR-TB isolates harbouring Met146Thr in Rv0678, which dated back to 2007, prior to the introduction of bedaquiline. High-level delamanid resistance was observed in two isolates with deletions in ddn, which were also resistant to pretomanid. Delamanid resistance was detected in two further isolates that harboured mutations in fbiA, but did not show cross-resistance to pretomanid. All isolates were susceptible to linezolid and clofazimine, and no mutations found were associated with resistance.

CONCLUSIONS: More studies that correlate genotypic and phenotypic drug susceptibility data are needed to increase the knowledge base of mutations associated with resistance, in particular for pretomanid. Overall, this study contributes to the development of future mutation catalogues for M. tuberculosis complex isolates.

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47. Meropenem-vaborbactam restoration of first-line drugs' efficacy and comparison of meropenem-vaborbactam-moxifloxacin versus BPaL MDR-TB regimen.

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Singh S(1), Gumbo T(2), Alffenaar JW(3), Boorgula GD(1), Thomas TA(4), Dheda K(5), Malinga L(6), Raj P(7), Aryal S(8), Srivastava S(9).

BACKGROUND: . To identify alternative treatment regimens for multi-drug resistant tuberculosis (MDR-TB), we tested meropenem in combination with β-lactamase inhibitors (BLIs) and other drugs.
METHODS: . We performed (1) MIC experiments, (2) static time-kill studies (STKs) with different BLIs, and (3) a hollow fiber model system of TB (HFS-TB) study with meropenem-vaborbactam combined with human equivalent daily doses of 20mg/kg or 35mg/kg rifampin, or moxifloxacin 400mg, or linezolid 600mg versus the bedaquiline-pretonamid-linezolid (BPaL) for MDR-TB. The studies were performed using the Mycobacterium tuberculosis (Mtb) H37Rv and an MDR-TB clinical strain (named Mtb16D) that underwent whole genome sequencing (WGS). Exponential decline models were used to calculate the kill rate constant (K) of different HFS-TB regimens.
RESULTS: . WGS revealed mutations associated with resistance to rifampin,

isoniazid, and cephalosporins. The meropenem-vaborbactam MIC of Mtb was H37Rv 2mg/L and >128 mg/L for Mtb 16D. Relebactam and vaborbactam improved both the potency and efficacy of meropenem in STKs. Meropenem-vaborbactam alone failed to kill Mtb16D but killed below day 0 burden when combined with isoniazid and rifampin, with moxifloxacin combination being the most effective and outranking bedaquiline and pretomanid. In the HFS-TB, meropenem-vaborbactam-moxifloxacin, and BPaL had the highest K (log10 cfu/mL/day) of 0.31 (95%CI: 0.17-0.58) and 0.34 (95%CI: 0.21-0.56), while meropenem-vaborbactam-rifampin (35mg/kg) had K of 0.18 (95%CI: 0.12-0.25). K for meropenem-vaborbactam-moxifloxacin-linezolid demonstrated antagonism.
CONCLUSION: . Adding meropenem-vaborbactam could potentially restore the efficacy of isoniazid and rifampin against MDR-TB. The meropenem-vaborbactam-moxifloxacin backbone regimen has implications for creating a new effective MDR-TB regimen.
IMPORTANCE: Tuberculosis (TB), caused by Mycobacterium tuberculosis (Mtb), remains a significant cause of mortality globally. The bedaquiline-pretonamid-linezolid (BPaL) regimen is effective against MDR-TB. However, the drugs in the regimen are also associated with adverse events. β-lactam antibiotics, including carbapenems, have shown efficacy against MDR-TB. Further pharmacokinetics/pharmacodynamics studies are needed to develop optimal dose combinations with other drugs to create alternate MDR-TB regimens. This study describes that the combination of β-lactam (meropenem) and β-lactamase inhibitor (vaborbactam) could restore the efficacy of isoniazid and rifampin against MDR-TB clinical strains, and the meropenem-vaborbactam-moxifloxacin combination has equal efficacy as the standard of care BPaL regimen for MDR-TB treatment.

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48. Microbial glycosylation of antitubercular agent chlorflavonin.

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Flavonoids have shown health-benefiting properties, such as antioxidative and anti-inflammatory activities, and are commonly used as nutraceuticals and pharmaceuticals. Although flavonoids are predominantly identified from plants, several filamentous fungal species have also been reported to produce bioactive flavonoids, including chlorflavonin from Aspergillus candidus, a novel

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

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