Literature

1. **Tuberculosis in pregnancy.**

Best Pract Res Clin Obstet Gynaecol. 2022 Dec;85(Pt A):34-44. doi: 10.1016/j.bpobgyn.2022.07.006. Epub 2022 Jul 31.

Hui SYA(1), Lao TT(2).

Due to COVID-19 pandemic, the latest progress of the End Tuberculosis (TB) Strategy was far from optimal and services for TB needs to be quickly restored. Pregnancy is a unique opportunity to screen and manage TB, and it is an essential step in TB eradication. Early diagnosis and treatment for active disease can reduce maternal and neonatal morbidities and mortality. The more widespread utilization of newer rapid molecular assays with drug-susceptibility testing has significantly shortened the diagnostic process for active TB disease. First-line anti-TB drugs are proven to be safe in pregnancy. Management of latent TB infection (LTBI) during pregnancy is controversial, but puerperium is a period of increased susceptibility to progress to active disease. Extrapulmonary TB (EPTB), multidrug-resistant TB (MDR-TB) and HIV co-infection remain significant issues surrounding TB management during pregnancy and often require input from a multidisciplinary team including TB experts.

DOI: 10.1016/j.bpobgyn.2022.07.006
PMCID: PMC9339097
PMID: 36002371 [Indexed for MEDLINE]

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

2. **Case-Finding Strategies for Drug-Resistant Tuberculosis: Protocol for a Scoping Review.**

JMIR Res Protoc. 2022 Dec 15;11(12):e40009. doi: 10.2196/40009.

Van Wyk SS(1), Nliwasa M(2), Seddon JA(3)(4), Hoddinott G(3), Viljoen L(3), Nepolo E(5), Günther G(5)(6), Ruswa N(7), Lin HH(8), Niemann S(9)(10)(11), Gandhi NR(12)(13), Shah NS(12)(13), Claassens M(5).

BACKGROUND: Transmission of drug-resistant tuberculosis (DR-TB) is ongoing. Finding individuals with DR-TB and initiating treatment as early as possible is

important to improve patient clinical outcomes and to break the chain of transmission to control the pandemic. To our knowledge systematic reviews assessing effectiveness, cost-effectiveness, acceptability, and feasibility of different case-finding strategies for DR-TB to inform research, policy, and practice have not been conducted, and it is unknown whether enough research exists to conduct such reviews. It is unknown whether case-finding strategies are similar for DR-TB and drug-susceptible TB and whether we can draw on findings from drug-susceptible reviews to inform decisions on case-finding strategies for DR-TB.
OBJECTIVE: This protocol aims to describe the available literature on case-finding for DR-TB and to describe case-finding strategies.
METHODS: We will screen systematic reviews, trials, qualitative studies, diagnostic test accuracy studies, and other primary research that specifically sought to improve DR-TB case detection. We will exclude studies that invited individuals seeking care for TB symptoms, those including individuals already diagnosed with TB, or laboratory-based studies. We will search the academic databases including MEDLINE, Embase, The Cochrane Library, Africa-Wide Information, CINAHL, Epistemonikos, and PROSPERO with no language or date restrictions. We will screen titles, abstracts, and full-text articles in duplicate. Data extraction and analyses will be performed using Excel (Microsoft Corp).
RESULTS: We will provide a narrative report with supporting figures or tables to summarize the data. A systems-based logic model, developed from a synthesis of case-finding strategies for drug-susceptible TB, will be used as a framework to describe different strategies, resulting pathways, and enhancements of pathways. The search will be conducted at the end of 2021. Title and abstract screening, full text screening, and data extraction will be undertaken from January to June 2022. Thereafter, analysis will be conducted, and results compiled.
CONCLUSIONS: This scoping review will chart existing literature on case-finding for DR-TB-this will help determine whether primary studies on effectiveness, cost-effectiveness, acceptability, and feasibility of different case-finding strategies for DR-TB exist and will help formulate potential questions for a systematic review. We will also describe case-finding strategies for DR-TB and how they fit into a model of case-finding pathways for drug-susceptible TB. This review has some limitations. One limitation is the diverse, inconsistent use of intervention terminology within the literature, which may result in missing relevant studies. Poor reporting of intervention strategies may also cause misunderstanding and misclassification of interventions. Lastly, case-finding strategies for DR-TB may not fit into a model developed from strategies for drug-susceptible TB. Nevertheless, such a situation will provide an opportunity to refine the model for future research. The review will guide further research to inform decisions on case-finding policies and practices for DR-TB.
INTERNATIONAL REGISTERED REPORT IDENTIFIER (IRRID): DERR1-10.2196/40009.

DOI: 10.2196/40009
PMCID: PMC9801265
PMID: 36520530

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

3. **The Changing Paradigm of Drug-Resistant Tuberculosis Treatment: Successes, Pitfalls, and Future Perspectives.**

Clin Microbiol Rev. 2022 Dec 21;35(4):e0018019. doi: 10.1128/cmr.00180-19. Epub 2022 Oct 6.

Dookie N(#)(1), Ngema SL(#)(1), Perumal R(1)(2), Naicker N(1)(2), Padayatchi N(1)(2), Naidoo K(1)(2).

Drug-resistant tuberculosis (DR-TB) remains a global crisis due to the increasing incidence of drug-resistant forms of the disease, gaps in detection and prevention, models of care, and limited treatment options. The DR-TB treatment landscape has evolved over the last 10 years. Recent developments include the remarkable activity demonstrated by the newly approved anti-TB drugs bedaquiline and pretomanid against Mycobacterium tuberculosis. Hence, treatment of DR-TB has drastically evolved with the introduction of the short-course regimen for multidrug-resistant TB (MDR-TB), transitioning to injection-free regimens and the approval of the 6-month short regimens for rifampin-resistant TB and MDR-TB. Moreover, numerous clinical trials are under way with the aim to reduce pill burden and shorten the DR-TB treatment duration. While there have been apparent successes in the field, some challenges remain. These include the ongoing inclusion of high-dose isoniazid in DR-TB regimens despite a lack of evidence for its efficacy and the inclusion of ethambutol and pyrazinamide in the standard short regimen despite known high levels of background resistance to both drugs. Furthermore, antimicrobial heteroresistance, extensive cavitary disease and intracavitary gradients, the emergence of bedaquiline resistance, and the lack of biomarkers to monitor DR-TB treatment response remain serious challenges to the sustained successes. In this review, we outline the impact of the new drugs and regimens on patient treatment outcomes, explore evidence underpinning current practices on regimen selection and duration, reflect on the disappointments and pitfalls in the field, and highlight key areas that require continued efforts toward improving treatment approaches and rapid biomarkers for

monitoring treatment response.

DOI: 10.1128/cmr.00180-19
PMCID: PMC9769521
PMID: 36200885 [Indexed for MEDLINE]

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

4. **Drug-Resistant Tuberculosis Treatment Outcomes among Children and Adolescents in Karachi, Pakistan.**

Trop Med Infect Dis. 2022 Dec 6;7(12):418. doi: 10.3390/tropicalmed7120418.

Malik AA(1), Khan U(1), Khan P(1)(2), Anwar A(3), Salahuddin N(3), Khowaja S(1), Khan AJ(1)(4)(5), Khan S(6), Hussain H(1), Amanullah F(3).

BACKGROUND: Significant data gaps exist for children and adolescents with drug-resistant (DR) TB, particularly from high TB incidence settings. This report provides a descriptive analysis of programmatic outcomes among children and adolescents treated for DR-TB in Pakistan.
METHODS: We extracted programmatic data from January 2014 to December 2019 from a tertiary care hospital with specialised child and adolescent DR-TB services. A physician assessed all children and adolescents (0-19 years) with presumptive DR-TB, including details of exposure to DR-TB, medical history, radiology, and laboratory results. All patients received treatment as per national DR-TB management guidelines based on WHO recommendations.
RESULTS: There were 262 treatment episodes for 247 patients enrolled during the study period. The median age of the cohort was 16 years (IQR: 13-18 years) with 16 (6.1%) children being under 5 years; 237 (90.5%) patients had pulmonary TB. The majority of the patients (194 or 74.1%) experienced a favourable treatment outcome and 26 (9.9%) died while on treatment. Female patients (78.5%) were more likely to experience favourable outcomes compared to males (64.7%; chi-sqr p-value = 0.02).
CONCLUSIONS: We found high rates of favourable outcomes in children and adolescents treated for DR-TB. However, there were few young children in our cohort and there was a considerable gender gap that enhanced efforts to diagnose DR-TB in young children and to elucidate and mitigate the reasons for poor outcomes amongst males.

DOI: 10.3390/tropicalmed7120418
PMCID: PMC9788275
PMID: 36548673

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

5. **Temporal trend of drug-resistant tuberculosis among Thai children during 2006-2021.**

IJID Reg. 2022 Sep 18;5:79-85. doi: 10.1016/j.ijregi.2022.09.005. eCollection 2022 Dec.

Jantarabenjakul W(1)(2), Supradish Na Ayudhya P(3), Suntarattiwong P(3), Thepnarong N(2), Rotcheewaphan S(4), Udomsantisuk N(4), Moonwong J(2), Kosulvit P(3), Tawan M(2), Sudjaritruk T(5)(6), Puthanakit T(1)(2).

BACKGROUND: The prevalence of drug-resistant tuberculosis (DR-TB) in adults has stabilized in the past decade. Our study aimed to describe the prevalence of DR-TB in Thai children between 2006 and 2021.
MATERIALS AND METHODS: Children younger than 15 years old who had culture-confirmed Mycobacterium tuberculosis complex (MTB), positive PCR-MTB, or positive Xpert MTB/RIF were included in this cohort. Drug susceptibility testing (DST) was performed using phenotypic and/or genotypic methods. The prevalence of DR-TB was compared using the chi-square test.
RESULTS: Among 163 confirmed TB cases (44% as pulmonary TB, 27% as extrapulmonary TB, and 29% with both), the median age (IQR) was 12.2 (7.3-14.2) years. DST was performed in 139 cases (85%), revealing prevalences of all DR-TB, isoniazid-resistant TB (Hr-TB), and rifampicin monoresistant/multidrug-resistant TB (Rr/MDR-TB) of 21.6% (95% CI 14.7-28.4), 10.8% (95% CI 5.6-16.0%), and 2.9% (95% CI 0.1-5.7%), respectively. The DR-TB rates did not differ significantly between 2006-2013, 2014-2018, and 2019-2021 ($p > 0.05$). Two pre-extensively DR-TB (pre-XDR) cases with fluoroquinolone resistance were detected after 2014.
CONCLUSION: The prevalence of DR-TB in Thai children was stable. However, one-tenth of DR-TB cases confirmed with DST were Hr-TB, which required adjustment of the treatment regimen. The pre-XDR cases should be closely monitored.

DOI: 10.1016/j.ijregi.2022.09.005
PMCID: PMC9550601
PMID: 36238580

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

6. **Pretomanid development and its clinical roles in treating tuberculosis.**

J Glob Antimicrob Resist. 2022 Dec;31:175-184. doi: 10.1016/j.jgar.2022.09.001. Epub 2022 Sep 8.

Fekadu G(1), Tolossa T(2), Turi E(2), Bekele F(3), Fetensa G(4).

Tuberculosis (TB) is the leading infectious cause of mortality worldwide. Despite the development of different antituberculosis drugs, managing resistant mycobacteria is still challenging. The discovery of novel drugs and new methods of targeted drug delivery have the potential to improve treatment outcomes, lower the duration of treatment, and reduce adverse events. Following bedaquiline and delamanid, pretomanid is the third medicine approved as part of a novel drug regimen for treating drug-resistant TB. It is a promising drug that has the capacity to shape TB treatment and achieve the End TB strategy set by the World Health Organization. The effectiveness of pretomanid has been reported in different observational and clinical studies. However, long-term safety data in humans are not yet available and the pretomanid-based regimen is recommended under an operational research framework that prohibits its wider and programmatic use. Further research is needed before pretomanid can be celebrated as a promising candidate for the treatment of different categories of TB and specific patients. This review covers the update on pretomanid development and its clinical roles in treating Mycobacterium tuberculosis.

DOI: 10.1016/j.jgar.2022.09.001
PMID: 36087906 [Indexed for MEDLINE]

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

Curr HIV/AIDS Rep. 2022 Dec;19(6):455-470. doi: 10.1007/s11904-022-00641-x. Epub 2022 Oct 29.

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

PURPOSE OF REVIEW: Pregnant people living with HIV (PLWH) are at especially high risk for progression from latent tuberculosis infection (LTBI) to active tuberculosis (TB) disease. Among pregnant PLWH, concurrent TB increases the risk of complications such as preeclampsia, intrauterine fetal-growth restriction, low birth weight, preterm-delivery, perinatal transmission of HIV, and admission to the neonatal intensive care unit. The grave impact of superimposed TB disease

on maternal morbidity and mortality among PLWH necessitates clear guidelines for concomitant therapy and an understanding of the pharmacokinetics (PK) and potential drug-drug interactions (DDIs) between antitubercular (anti-TB) agents and antiretroviral therapy (ART) in pregnancy.
RECENT FINDINGS: This review discusses the currently available evidence on the use of anti-TB agents in pregnant PLWH on ART. Pharmacokinetic and safety studies of anti-TB agents during pregnancy and postpartum are limited, and available data on second-line and newer anti-TB agents used in pregnancy suggest that several research gaps exist. DDIs between ART and anti-TB agents can decrease plasma concentration of ART, with the potential for perinatal transmission of HIV. Current recommendations for the treatment of LTBI, drug-susceptible TB, and multidrug-resistant TB (MDR-TB) are derived from observational studies and case reports in pregnant PLWH. While the use of isoniazid, rifamycins, and ethambutol in pregnancy and their DDIs with various ARTs are well-characterized, there is limited data on the use of pyrazinamide and several new and second-line antitubercular drugs in pregnant PLWH. Further research into treatment outcomes, PK, and safety data for anti-TB agent use during pregnancy and postpartum is urgently needed.

DOI: 10.1007/s11904-022-00641-x
PMCID: PMC9617238
PMID: 36308580 [Indexed for MEDLINE]

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

8. **Pre-extensively drug-resistant tuberculosis among multidrug-resistant tuberculosis patients in Ethiopia: a laboratory-based surveillance study.**

IJID Reg. 2022 Aug 30;5:39-43. doi: 10.1016/j.ijregi.2022.08.012. eCollection 2022 Dec.

Diriba G(1), Alemu A(1), Tola HH(2), Yenew B(1), Amare M(1), Eshetu K(3), Sinshaw W(1), Abebaw Y(1), Meaza A(1), Seid G(1), Moga S(1), Zerihun B(1), Getu M(1), Dagne B(1), Mollalign H(1), Tadesse M(1), Buta B(1), Wordofa N(1), Alemu E(1), Erresso A(1), Hailu M(1), Tefera Z(1), Wondimu A(1), Belhu T(1), Gamtesa DF(1), Getahun M(1), Kebede A(4), Abdela S(1).

BACKGROUND: The rise of drug-resistant tuberculosis (DR-TB) has presented a substantial challenge to the national tuberculosis (TB) control program. Understanding the epidemiology of pre-extensively drug-resistant tuberculosis

(pre-XDR-TB) could help clinicians to adapt MDR-TB treatment regimens at an earlier stage. This study aimed to assess second-line anti-TB drug resistance among MDR-TB patients in Ethiopia using routine laboratory-based data.
METHODS: Laboratory-based cross-sectional data were collected from the national TB reference laboratory and seven regional tuberculosis culture laboratories in Ethiopia from July 2019 to March 2022. The required data, such as drug-susceptibility testing (DST) results and sociodemographics, were collected on a structured checklist from laboratory registration books and electronic databases. Data were entered into a Microsoft Excel spreadsheet and analyzed using SPSS version 23. Descriptive statistics were performed to show the distribution and magnitude of drug resistance.
RESULTS: Second-line drugs (SLDs) susceptibility testing was performed for 644 MDR isolates, of which 19 (3%) were found to be pre-XDR-TB cases. Of the total MDR-TB isolates, 19 (3%) were resistant to at least one fluoroquinolone drug, while 11 (1.7%) were resistant to at least one injectable second-line drug. Of the 644 MDR-TB isolates, 1.9% (5/261) pre-XDR were from new MDR-TB cases, while 3.7% (14/383) were from previously treated MDR-TB patients. The most frequently identified mutations, based on MTBDRsl results, were in codon A90V of the gyrA gene (77.3%) and A1401G of the rrs gene (45.5%).
CONCLUSION: The overall prevalence of pre-XDR-TB in Ethiopia is considerable. The majority of SLD resistance mutations were in the gyrA gene at position A90V. Modern, rapid DST is necessary to enable identification of pre-XDR-TB and XDR-TB in supporting proper regimen administration for patients.

DOI: 10.1016/j.ijregi.2022.08.012
PMCID: PMC9513164
PMID: 36176268

9. **Rapid Diagnosis of XDR and Pre-XDR TB: A Systematic Review of Available Tools.**

Arch Bronconeumol. 2022 Dec;58(12):809-820. doi: 10.1016/j.arbres.2022.07.012. Epub 2022 Jul 28.

[Article in English, Spanish]

Saderi L(1), Puci M(1), Di Lorenzo B(1), Centis R(2), D'Ambrosio L(3), Akkerman OW(4), Alffenaar JC(5), Caminero JA(6), Chakaya JM(7), Denholm JT(8), Kurhasani X(9), Ong CWM(10), Rendon A(11), Silva DR(12), Tiberi S(13), Zenner D(14), Cabibbe AM(15), Migliori GB(16), Sotgiu G(1).

INTRODUCTION: No previous systematic reviews have comprehensively investigated

the features of Xpert MTB/XDR and other rapid tests to diagnose pre-XDR/XDR-TB. The aim of this systematic review is to assess existing rapid diagnostics for pre-XDR/XDR-TB from a point-of-care perspective and describe their technical characteristics (i.e., sensitivity, specificity, positive and negative predictive values).
METHODS: Embase, PubMed, Scopus, and Web of Science were searched to detect the articles focused on the accuracy of commercially available rapid molecular diagnostic tests for XDR-TB according to PRISMA guidelines. The analysis compared the diagnostic techniques and approaches in terms of sensitivity, specificity, laboratory complexity, time to confirmed diagnosis.
RESULTS: Of 1298 records identified, after valuating article titles and abstracts, 97 (7.5%) records underwent full-text evaluation and 38 records met the inclusion criteria. Two rapid World Health Organization (WHO)-endorsed tests are available: Xpert MTB/XDR and GenoType MTBDRsl (VER1.0 and VER 2.0). Both tests had similar performance, slightly favouring Xpert, although only 2 studies were available (sensitivity 91.4-94; specificity 98.5-99; accuracy 97.2-97.7; PPV 88.9-99.1; NPV 95.8-98.9).
CONCLUSIONS: Xpert MTB/XDR could be suggested at near-point-of-care settings to be used primarily as a follow-on test for laboratory-confirmed TB, complementing existing rapid tests detecting at least rifampicin-resistance. Both Xpert MTB/XDR and GenoType MTBDRsl are presently diagnosing what WHO defined, in 2021, as pre-XDR-TB.

DOI: 10.1016/j.arbres.2022.07.012
PMID: 35945071 [Indexed for MEDLINE]

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

Am J Trop Med Hyg. 2022 Oct 31;107(6):1295-1301. doi: 10.4269/ajtmh.22-0294. Print 2022 Dec 14.

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

Drug-resistant tuberculosis (DR-TB) continues to be a serious public health problem. The objective of this study was to evaluate the sociodemographic, radiological, clinical, and outcome characteristics and assess the determinants of unfavorable outcomes in DR-TB. The descriptive-analytical study was carried

out in a reference outpatient clinic in Rio de Janeiro, Brazil, among DR-TB cases that received treatment between February 2016 and October 2020, using descriptive statistics, χ2 test, and logistic regression multivariate. Of the 148 cases, 12.2% were resistant to rifampicin, 12.2% were resistant to isoniazid, 18.2% were polyresistant, 56.1% multidrug resistant, and 1.3% were extensively drug resistant. Most of the patients were men, aged up to 44 years, with brown or black skin, having up to 8 years of schooling, unemployed or working in the informal economy, and of low income. Presenting with acquired resistance or positive sputum smear microscopy in the diagnosis, taking more than four drugs, and being unemployed were associated with unfavorable outcomes. Having no income or acquired resistance doubled the chances of unfavorable outcomes. There was a high proportion of unfavorable outcomes, thereby highlighting the need to concentrate efforts on planning and executing public policies that include the severity of DR-TB and its risk factors.

DOI: 10.4269/ajtmh.22-0294
PMCID: PMC9768274
PMID: 36316000 [Indexed for MEDLINE]

11. **Comparative genomics of drug-resistant strains of Mycobacterium tuberculosis in Ecuador.**

BMC Genomics. 2022 Dec 21;23(1):844. doi: 10.1186/s12864-022-09042-1.

Morey-León G(1)(2)(3), Andrade-Molina D(4), Fernández-Cadena JC(4), Berná L(5)(6).

BACKGROUND: Tuberculosis is a serious infectious disease affecting millions of people. In spite of efforts to reduce the disease, increasing antibiotic resistance has contributed to persist in the top 10 causes of death worldwide. In fact, the increased cases of multi (MDR) and extreme drug resistance (XDR) worldwide remains the main challenge for tuberculosis control. Whole genome sequencing is a powerful tool for predicting drug resistance-related variants, studying lineages, tracking transmission, and defining outbreaks. This study presents the identification and characterization of resistant clinical isolates of Mycobacterium tuberculosis including a phylogenetic and molecular resistance profile study by sequencing the complete genome of 24 strains from different provinces of Ecuador.
RESULTS: Genomic sequencing was used to identify the variants causing resistance. A total of 15/21 isolates were identified as MDR, 4/21 as pre-XDR and 2/21 as XDR, with three isolates discarded due to low quality; the main sub-lineage was LAM (61.9%) and Haarlem (19%) but clades X, T and S were identified. Of the six pre-XDR and XDR strains, it is noteworthy that five come

from females; four come from the LAM sub-lineage and two correspond to the X-class sub-lineage. A core genome of 3,750 genes, distributed in 295 subsystems, was determined. Among these, 64 proteins related to virulence and implicated in the pathogenicity of M. tuberculosis and 66 possible pharmacological targets stand out. Most variants result in nonsynonymous amino acid changes and the most frequent genotypes were identified as conferring resistance to rifampicin, isoniazid, ethambutol, para-aminosalicylic acid and streptomycin. However, an increase in the resistance to fluoroquinolones was detected.
CONCLUSION: This work shows for the first time the variability of circulating resistant strains between men and women in Ecuador, highlighting the usefulness of genomic sequencing for the identification of emerging resistance. In this regard, we found an increase in fluoroquinolone resistance. Further sampling effort is needed to determine the total variability and associations with the metadata obtained to generate better health policies.

DOI: 10.1186/s12864-022-09042-1
PMCID: PMC9769008
PMID: 36544084 [Indexed for MEDLINE]

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

12. **Bacteriophages of Mycobacterium tuberculosis, their diversity, and potential therapeutic uses: a review.**

BMC Infect Dis. 2022 Dec 22;22(1):957. doi: 10.1186/s12879-022-07944-9.

Zeynali Kelishomi F(1), Khanjani S(1), Fardsanei F(1), Saghi Sarabi H(1), Nikkhahi F(2), Dehghani B(3).

Tuberculosis (TB) caused by Mycobacterium tuberculosis (M. tuberculosis) is a highly infectious disease and worldwide health problem. Based on the WHO TB report, 9 million active TB cases are emerging, leading to 2 million deaths each year. The recent emergence of multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) strains emphasizes the necessity to improve novel therapeutic plans. Among the various developing antibacterial approaches, phage therapy is thought to be a precise hopeful resolution. Mycobacteriophages are viruses that infect bacteria such as Mycobacterium spp., containing the M. tuberculosis complex. Phages and phage-derived proteins can act as promising antimicrobial agents. Also, phage

cocktails can broaden the spectrum of lysis activity against bacteria. Recent researches have also shown the effective combination of antibiotics and phages to defeat the infective bacteria. There are limitations and concerns about phage therapy. For example, human immune response to phage therapy, transferring antibiotic resistance genes, emerging resistance to phages, and safety issues. So, in the present study, we introduced mycobacteriophages, their use as therapeutic agents, and their advantages and limitations as therapeutic applications.

DOI: 10.1186/s12879-022-07944-9
PMCID: PMC9773572
PMID: 36550444 [Indexed for MEDLINE]

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

13. **The effect of undernutrition on sputum culture conversion and treatment outcomes among people with multidrug-resistant tuberculosis: a systematic review and meta-analysis.**

Int J Infect Dis. 2022 Dec 6;127:93-105. doi: 10.1016/j.ijid.2022.11.043. Online ahead of print.

Wagnew F(1), Alene KA(2), Kelly M(3), Gray D(4).

OBJECTIVES: We aimed to evaluate the effect of undernutrition on sputum culture conversion and treatment outcomes among people with multidrug-resistant tuberculosis (MDR-TB).
METHODS: We searched for publications in the Medline, Embase, Scopus, and Web of Science databases. We conducted a random-effect meta-analysis to estimate the effects of undernutrition on sputum culture conversion and treatment outcomes. Hazard ratio (HR) for sputum culture conversion and odds ratio (OR) for end-of-treatment outcomes, with 95% CI, were used to summarize the effect estimates. Potential publication bias was checked using funnel plots and Egger's tests.
RESULTS: Of the 2358 records screened, 63 studies comprising a total of 31,583 people with MDR-TB were included. Undernutrition was significantly associated with a longer time to sputum culture conversion (HR 0.7, 95% CI 0.6-0.9, I2 = 67·1%), and a higher rate of mortality (OR 2.8, 95% CI 2.1-3.6, I2 = 21%) and unsuccessful treatment outcomes (OR 1.8, 95% CI 1.5-2.1, I2 = 70%). There was no significant publication bias in the included studies.
CONCLUSION: Undernutrition was significantly associated with unsuccessful

treatment outcomes, including mortality and longer time to sputum culture conversion among people with MDR-TB. These findings have implications for supporting targeted nutritional interventions alongside standardized TB drugs.

DOI: 10.1016/j.ijid.2022.11.043
PMID: 36481489

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

14. **Availability and costs of medicines for the treatment of tuberculosis in Europe.**

Clin Microbiol Infect. 2023 Jan;29(1):77-84. doi: 10.1016/j.cmi.2022.07.026. Epub 2022 Aug 10.

Günther G(1), Guglielmetti L(2), Leu C(3), Lange C(4), van Leth F(5); Tuberculosis Network European Trials group.

Collaborators: Hasan Hafizi(6), Khachatryan N(7), Aroyan H(7), Kabasakalyan E(8), Knappik M(9), Skrahina A(10), Klimuk D(10), Nikolenka A(10), Muylle I(11), Milanov V(12), Velkovska D(13), Tarinska N(13), Bachiyska E(14), Jankovic M(15), Pieridou D(16), Adamide T(17), Nicolaou N(18), Vasakova M(19), Sukholytka M(19), Kopeckà E(20), Folkvardsen DB(21), Svensson E(21), Danilovits M(22), Kummik T(23), Vasankari T(24), Fréchet-Jachym M(25), Nahmiash A(25), Togonidze T(26), Avaliani Z(26), Kinkladze I(26), Aspindzelashvili R(26), Bichashvili T(26), Losaberidze G(26), Merabishvili T(26), Kalsdorf B(27), Manika K(28), Tsiakitzis K(29), Bakos A(30), Ægisdóttir TR(31), Michelsen GS(31), Karlsdóttir K(31), McLaughlin AM(32), Fitzgibbon M(33), Chemtob D(34), Codecasa LR(35), Ferrarese M(35), Torri S(35), Gjocaj M(36), Kuksa L(37), Davidaviciene E(38), Wirtz G(39), Perrin M(40), Asciak AP(41), Chesov D(42), de Lange W(43), Akkerman O(43), Poposka BI(44), Mack U(45), Jensenius M(46), Kvalvik L(47), Mengshoel AT(48), Kruczak K(49), Duarte R(50), Ribeiro N(51), Ibraim E(52), Kaluzhenina A(53), Barkanova O(53), Pesut D(54), Solovic I(55), Svetina P(56), Souza-Galvão ML(57), Millet JP(58), Casas X(59), Vives M(59), Bruchfeld J(60), Dalemo P(61), Jonsson J(62), Aeschbacher K(63), Keller P(64), Özkara S(65), Tiberi S(66), Chen C(67), Terleeva Y(68), Dudnyk A(69).

OBJECTIVES: To evaluate the access to comprehensive diagnostics and novel antituberculosis medicines in European countries.
METHODS: We investigated the access to genotypic and phenotypic Mycobacterium tuberculosis drug susceptibility testing and the availability of

antituberculosis drugs and calculated the cost of drugs and treatment regimens at major tuberculosis treatment centres in countries of the WHO European region where rates of drug-resistant tuberculosis are the highest among all WHO regions. Results were stratified by middle-income and high-income countries.
RESULTS: Overall, 43 treatment centres from 43 countries participated in the study. For WHO group A drugs, the frequency of countries with the availability of phenotypic drug susceptibility testing was as follows: (a) 75% (30/40) for levofloxacin, (b) 82% (33/40) for moxifloxacin, (c) 48% (19/40) for bedaquiline, and (d) 72% (29/40) for linezolid. Overall, of the 43 countries, 36 (84%) and 24 (56%) countries had access to bedaquiline and delamanid, respectively, whereas only 6 (14%) countries had access to rifapentine. The treatment of patients with extensively drug-resistant tuberculosis with a regimen including a carbapenem was available only in 17 (40%) of the 43 countries. The median cost of regimens for drug-susceptible tuberculosis, multidrug-resistant/rifampicin-resistant tuberculosis (shorter regimen, including bedaquiline for 6 months), and extensively drug-resistant tuberculosis (including bedaquiline, delamanid, and a carbapenem) were €44 (minimum-maximum, €15-152), €764 (minimum-maximum, €542-15152), and €8709 (minimum-maximum, €7965-11759) in middle-income countries (n = 12) and €280 (minimum-maximum, €78-1084), €29765 (minimum-maximum, €11116-40584), and €217591 (minimum-maximum, €82827-320146) in high-income countries (n = 29), respectively.
DISCUSSION: In countries of the WHO European region, there is a widespread lack of drug susceptibility testing capacity to new and repurposed antituberculosis drugs, lack of access to essential medications in several countries, and a high cost for the treatment of drug-resistant tuberculosis.

DOI: 10.1016/j.cmi.2022.07.026
PMCID: PMC9801521
PMID: 35961488 [Indexed for MEDLINE]

Conflict of interest statement: Transparency declaration CLa provided consultation service to INSMED and received speaker's honoraria from INSMED, GILEAD, and JANSSEN, outside of the scope of this work. The other authors declare that they have no conflicts of interest. CLa is supported by the German Center for Infection Research (DZIF). All other authors have no funding source in the context of this manuscript.

15. **Genotypic Distribution and the Epidemiology of Multidrug Resistant Tuberculosis in Upper Northern Thailand.**

Antibiotics (Basel). 2022 Dec 1;11(12):1733. doi: 10.3390/antibiotics11121733.

Saikaew S(1)(2), Thongprachum A(1), Pongsararuk R(3), Thanraka A(4), Kunyanone N(4), Chaiyasirinroje B(5), Luangsook P(2)(6), Butr-Indr B(2)(6), Phunpae P(2)(6), Wattananandkul U(2)(6)(7).

The epidemiology and genotypes of multidrug-resistant tuberculosis (MDR-TB), a global public health threat, remain limited. The genotypic distribution and factors associated with MDR-TB in upper northern Thailand between 2015 and 2019 were investigated. The DNA sequencing of rpoB, katG, and inhA promoter of 51 multidrug-resistant Mycobacterium tuberculosis isolates revealed nine patterns of the rpoB gene mutation distributed in seven provinces. The S531L mutation was the most common mutation in all provinces. The rpoB mutation in Chiang Rai, Chiang Mai, and Lampang was highly diverse compared to other areas. Here, the mutation profiles that have yet to be reported in northern Thailand (H526P, Q513P, and H526C) were detected in Chiang Rai province. The S315T katG mutation was the most common genotype associated with INH resistance, especially in Chiang Mai and Lampang. Further analysis of data from 110 TB patients (42 MDR-TB and 68 drug-susceptible TB) revealed that <60 years of age was a significant factor associated with MDR-TB (OR = 0.316, 95% CI 0.128-0.784, p = 0.011) and ≥60 years of age was a significant factor associated with the S315T katG-mutation (OR = 8.867, 95% CI 0.981-80.177, p = 0.047). This study highlighted the necessity for continuous surveillance and risk factor monitoring for effective control of MDR-TB.

DOI: 10.3390/antibiotics11121733
PMCID: PMC9774302
PMID: 36551389

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

16. **Distribution of Mycobacterium tuberculosis Lineages and Drug Resistance in Upper Myanmar.**

Trop Med Infect Dis. 2022 Dec 19;7(12):448. doi: 10.3390/tropicalmed7120448.

Phyu AN(1)(2), Aung ST(3), Palittapongarnpim P(4), Htet KKK(2), Mahasirimongkol S(5), Aung HL(6), Chaiprasert A(7), Chongsuvivatwong V(2).

Mycobacterium tuberculosis complex (MTBC) is divided into 9 whole genome sequencing (WGS) lineages. Among them, lineages 1-4 are widely distributed. Multi-drug resistant tuberculosis (MDR-TB) is a major public health threat. For effective TB control, there is a need to obtain genetic information on lineages of Mycobacterium tuberculosis (Mtb) and to understand distribution of lineages

and drug resistance. This study aimed to describe the distribution of major lineages and drug resistance patterns of Mtb in Upper Myanmar. This was a cross-sectional study conducted with 506 sequenced isolates. We found that the most common lineage was lineage 2 (n = 223, 44.1%). The most common drug resistance mutation found was streptomycin (n = 44, 8.7%). Lineage 2 showed a higher number of MDR-TB compared to other lineages. There were significant associations between lineages of Mtb and drug resistance patterns, and between lineages and geographical locations of Upper Myanmar (p value < 0.001). This information on the distribution of Mtb lineages across the geographical areas will support a lot for the better understanding of TB transmission and control in Myanmar and other neighboring countries. Therefore, closer collaboration in cross border tuberculosis control is recommended.

DOI: 10.3390/tropicalmed7120448
PMCID: PMC9781755
PMID: 36548703

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

17. **Drug Resistance and Molecular Characteristics of Mycobacterium tuberculosis: A Single Center Experience.**

J Pers Med. 2022 Dec 19;12(12):2088. doi: 10.3390/jpm12122088.

Li S(1), Chen W(1), Feng M(1), Liu Y(1), Wang F(1).

In recent years, the incidence of tuberculosis (TB) and mortality caused by the disease have been decreasing. However, the number of drug-resistant tuberculosis patients is increasing rapidly year by year. Here, a total of 380 Mycobacterium tuberculosis (MTB)-positive formalin-fixed and paraffin-embedded tissue (FFPE) specimens diagnosed in the Department of Pathology of the Eighth Medical Center, Chinese PLA General Hospital were collected. Among 380 cases of MTB, 85 (22.37%) were susceptible to four anti-TB drugs and the remaining 295 (77.63%) were resistant to one or more drugs. The rate of MDR-TB was higher in previously treated cases (52.53%) than in new cases [(36.65%), p < 0.05]. Of previously treated cases, the rate of drug resistance was higher in females than in males (p < 0.05). Among specimens obtained from males, the rate of drug resistance was higher in new cases than in previously treated cases (p < 0.05). Of mutation in drug resistance-related genes, the majority (53/380, 13.95%) of rpoB gene carried the D516V mutation, and 13.42% (51/380) featured mutations in both the katG and inhA genes. Among the total specimens, 18.68% (71/380) carried the 88 M mutation in the rpsL gene, and the embB gene focused on the 306 M2 mutation with a mutation rate of 19.74%. Among the resistant INH,

the mutation rate of -15 M was higher in resistance to more than one drug than in monodrug-resistant (p < 0.05). In conclusion, the drug resistance of MTB is still very severe and the timely detection of drug resistance is conducive to the precise treatment of TB.

DOI: 10.3390/jpm12122088
PMCID: PMC9783070
PMID: 36556308

Conflict of interest statement: The author declares no conflict of interest.

18. **Tuberculosis Infection in Pregnant People: Current Practices and Research Priorities.**

Pathogens. 2022 Dec 6;11(12):1481. doi: 10.3390/pathogens11121481.

Mathad JS(1)(2), Yadav S(1), Vaidyanathan A(1), Gupta A(3), LaCourse SM(4).

Women are significantly more likely to develop tuberculosis (TB) disease within the first 90 days after pregnancy than any other time in their lives. Whether pregnancy increases risk of progression from TB infection (TBI) to TB disease is unknown and is an active area of investigation. In this review, we discuss the epidemiology of TB and TBI in pregnancy, TBI diagnostics, and prevalence in pregnancy. We also review TBI treatment and highlight research priorities, such as short-course TB prevention regimens, drug-resistant TB prevention, and additional considerations for safety, tolerability, and pharmacokinetics that are unique to pregnant and postpartum people.

DOI: 10.3390/pathogens11121481
PMCID: PMC9782762
PMID: 36558815

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

19. **Prevalence of Multidrug-Resistant TB Among Smear-Positive Pulmonary TB Patients in Banadir, Somalia: A Multicenter Study.**

Infect Drug Resist. 2022 Dec 10;15:7241-7248. doi: 10.2147/IDR.S386497. eCollection 2022.

Dirie AMH(1), Çolakoğlu S(1), Abdulle OM(2), Abdi BM(3), Osman MA(4), Shire AM(5), Hussein AM(6).

BACKGROUND: Tuberculosis (TB) is an infectious disease that is the second most common cause of death from a single infectious agent. TB infection affects anyone, regardless of age, gender, and ethnicity. Drug-resistant TB is a serious public health problem, which needs treatment with a second-line anti-TB drug and it includes poly-drug resistance (PDR), multi-drug resistance (MDR), and extensive drug resistance (XDR). The goal of this research is to find out the prevalence of MDR TB among pulmonary TB patients in Banadir, Somalia.
METHODS: This was a multicenter retrospective review of data involving 1732 smear-positive pulmonary TB patients visiting Banadir TB centers between July 1, 2019 and June 30, 2020. Demographic, clinical, and drug susceptibility data were retrieved from TB treatment cards. The data were analyzed using Statistical Package for Social Sciences (SPSS) software (IBM SPSS Statistics version 26).
RESULTS: All 1732 pulmonary TB cases were previously diagnosed by the Gene Xpert MTB/RIF test. Among them, 70.4% (1219/1732) were males. The mean age was 31.77 years. Overall, the prevalence of drug resistance TB was 10.56% (183/1732). The MDR TB was 1.96%, poly-drug resistance (PDR) was 0.12%, and extensive drug resistance was 0.06%.
CONCLUSION: This study showed a prevalence of MDR-TB among pulmonary TB patients, which is similar to some of the eastern African countries.

DOI: 10.2147/IDR.S386497
PMCID: PMC9749408
PMID: 36533250

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

20. **Ultrasensitive Detection of Multidrug-Resistant Mycobacterium tuberculosis Using SuperSelective Primer-Based Real-Time PCR Assays.**

Int J Mol Sci. 2022 Dec 12;23(24):15752. doi: 10.3390/ijms232415752.

Narang A(1), Marras SAE(1), Kurepina N(2), Chauhan V(3), Shashkina E(2), Kreiswirth B(2), Varma-Basil M(3), Vinnard C(4), Subbian S(1).

The emergence of drug-resistant tuberculosis is a significant global health issue. The presence of heteroresistant Mycobacterium tuberculosis is critical to developing fully drug-resistant tuberculosis cases. The currently available molecular techniques may detect one copy of mutant bacterial genomic DNA in the presence of about 1-1000 copies of wild-type M. tuberculosis DNA. To improve the

limit of heteroresistance detection, we developed SuperSelective primer-based real-time PCR assays, which, by their unique assay design, enable selective and exponential amplification of selected point mutations in the presence of abundant wild-type DNA. We designed SuperSelective primers to detect genetic mutations associated with M. tuberculosis resistance to the anti-tuberculosis drugs isoniazid and rifampin. We evaluated the efficiency of our assay in detecting heteroresistant M. tuberculosis strains using genomic DNA isolated from laboratory strains and clinical isolates from the sputum of tuberculosis patients. Results show that our assays detected heteroresistant mutations with a specificity of 100% in a background of up to 104 copies of wild-type M. tuberculosis genomic DNA, corresponding to a detection limit of 0.01%. Therefore, the SuperSelective primer-based RT-PCR assay is an ultrasensitive tool that can efficiently diagnose heteroresistant tuberculosis in clinical specimens and contributes to understanding the drug resistance mechanisms. This approach can improve the management of antimicrobial resistance in tuberculosis and other infectious diseases.

DOI: 10.3390/ijms232415752
PMCID: PMC9779475
PMID: 36555395 [Indexed for MEDLINE]

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

21. **Factors Related to Complying with Anti-TB Medications Among Drug-Resistant Tuberculosis Patients in Indonesia.**

Patient Prefer Adherence. 2022 Dec 17;16:3319-3327. doi: 10.2147/PPA.S388989. eCollection 2022.

Yani DI(1), Juniarti N(1), Lukman M(1).

BACKGROUND: A variety of factors influenced the decision of tuberculosis (TB) drug-resistant patients to continue treatment. The study aimed to analyze factors that influence complying with anti-TB medications in patients with TB drug resistance in Indonesia.
PATIENTS AND METHODS: The study employed a cross-sectional approach and was conducted in various community health centers and polyclinics offering TB drug-resistant services in Bandung city, Indonesia. Participants were 79 patients with TB drug resistance who met the criteria during their treatment for TB drug resistance, were willing to be involved in the research, and accessed TB services in Bandung. Complying with anti-TB medications scale, TB Health Behaviors questionnaire, the family support questionnaire, the TB-Related Stigma

Scale, and TB knowledge were used in this study. Data were analyzed using Spearman's Rho.
RESULTS: Health behavior (r = 0.36) was positively associated with complying with anti-TB medications, while family support, TB stigma, and knowledge were not related to treatment compliance.
CONCLUSION: Information on these factors will inform the development of models and modules for the prevention and control of TB drug resistance in Indonesia, which can later be used widely in Indonesia.

DOI: 10.2147/PPA.S388989
PMCID: PMC9769133
PMID: 36568917

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

22. **A systematic review on extensively drug-resistant tuberculosis from 2009 to 2020: special emphases on treatment outcomes.**

Rev Esp Quimioter. 2022 Dec 9:shiromwar09dec2022. doi: 10.37201/req/029.2022. Online ahead of print.

Shiromwar SS(1), Khan AH, Chidrawar V.

OBJECTIVE: Extensively drug-resistant tuberculosis (XDR-TB) has raised a great threat to human health globally, especially in developing countries. The objective of the present study is to collate and contrast the proportions of treatment outcome in the previously published XDR-TB articles.
METHODS: By considering inclusion criteria and search engines, a total of 22 articles were enrolled.
RESULTS: Our findings revealed that the overall favorable treatment outcome was 24.04%. From the cohort of enrolled studies 19.76% (397) and 43.35% (871) patients were cured and died respectively. In 90.9% of enrolled articles, the investigators performed drug-susceptibility testing at the baseline. The overall treatment outcome was improved by the use of new drugs (linezolid, bedaquiline, ciprofloxacin, clofazimine) in the treatment regimen of XDR-TB showing linezolid and bedaquiline better results i.e. 59.44 and 78.88%, respectively. Moreover, use of antiretroviral treatment in XDR-TB patients with HIV infection have not shown any significant difference in the treatment outcome.
CONCLUSIONS: XDR-TB treatment success can be achieved by implying standardized definitions, upgraded diagnostic procedures, and novel drugs.

DOI: 10.37201/req/029.2022
PMID: 36503203

23. **Exopolyphosphatases PPX1 and PPX2 from Mycobacterium tuberculosis regulate dormancy response and pathogenesis.**

Microb Pathog. 2022 Dec;173(Pt B):105885. doi: 10.1016/j.micpath.2022.105885. Epub 2022 Nov 18.

Tiwari P(1), Gosain TP(2), Chugh S(2), Singh M(2), Sankhe GD(3), Arora G(2), Kidwai S(2), Agarwal S(2), Saini DK(4), Singh R(5).

Stress adaptation and virulence of various bacterial pathogens require stringent response pathways involving guanosine pentaphosphate and inorganic polyphosphate (PolyP). In M. tuberculosis, intracellular PolyP levels are maintained by the activities of polyphosphate kinase (PPK-1, PPK-2) and exopolyphosphatases (PPX-1, PPX-2). We demonstrate that these exopolyphosphatases cumulatively contribute to biofilm formation and survival of M. tuberculosis in nutrient limiting, low oxygen growth conditions and in macrophages. Characterization of single (Δppx2) and double knock out strain (dkppx) of M. tuberculosis demonstrated that these exopolyphosphatases are essential for establishing infection in guinea pigs and mice. Transcriptional profiling revealed that relative to the parental strain the expression of genes belonging to DosR regulon were significantly reduced in mid-log phase cultures of dkppx strain. We also show that PolyP inhibited the autophosphorylation activities associated with DosT and DosS sensor kinases. Host RNA-seq analysis revealed that transcripts involved in various antimicrobial pathways such as apoptosis, autophagy, macrophage activation, calcium signalling, innate and T-cell response were differentially expressed in lung tissues of dkppx strain infected mice. Taken together, we demonstrate that enzymes involved in PolyP homeostasis play a critical role in physiology and virulence of M. tuberculosis. These enzymes are attractive targets for developing novel interventions that might be active against drug-sensitive and drug-resistant M. tuberculosis.

DOI: 10.1016/j.micpath.2022.105885

PMID: 36403711 [Indexed for MEDLINE]

Conflict of interest statement: Declaration of competing interest The authors declare no competing interest exists.

24. **Paediatric formulations for the treatment of drug resistant TB: closing the gaps.**

Int J Tuberc Lung Dis. 2022 Dec 1;26(12):1097-1100. doi: 10.5588/ijtld.22.0498.

Alffenaar JWC(1), Marais BJ(2), Touw DJ(3).

DOI: 10.5588/ijtld.22.0498
PMCID: PMC9728946
PMID: 36447327 [Indexed for MEDLINE]

25. **Disadvantage and the Experience of Treatment for Multidrug-Resistant Tuberculosis (MDR-TB).**

SSM Qual Res Health. 2022 Dec;2:100042. doi: 10.1016/j.ssmqr.2022.100042. Epub 2022 Jan 28.

Taylor HA(1), Dowdy DW(2), Searle AR(3), Stennett AL(3), Dukhanin V(1), Zwerling AA(4), Merritt MW(5).

DOI: 10.1016/j.ssmqr.2022.100042
PMCID: PMC8896740
PMID: 35252955

Conflict of interest statement: Declarations of Conflicts of Interest: None

26. **Dynamic (18)F-Pretomanid PET imaging in animal models of TB meningitis and human studies.**

Nat Commun. 2022 Dec 29;13(1):7974. doi: 10.1038/s41467-022-35730-3.

Mota F(#)(1)(2)(3), Ruiz-Bedoya CA(#)(1)(2)(3), Tucker EW(#)(1)(2)(4), Holt DP(#)(5), De Jesus P(1)(2)(3), Lodge MA(5), Erice C(1)(2)(4), Chen X(1)(2)(3), Bahr M(1)(2)(3), Flavahan K(1)(2)(3), Kim J(1)(2)(4), Brosnan MK(5), Ordonez AA(1)(2)(3), Peloquin CA(6), Dannals RF(5), Jain SK(7)(8)(9)(10).

Pretomanid is a nitroimidazole antimicrobial active against drug-resistant Mycobacterium tuberculosis and approved in combination with bedaquiline and linezolid (BPaL) to treat multidrug-resistant (MDR) pulmonary tuberculosis (TB). However, the penetration of these antibiotics into the central nervous system (CNS), and the efficacy of the BPaL regimen for TB meningitis, are not well established. Importantly, there is a lack of efficacious treatments for TB meningitis due to MDR strains, resulting in high mortality. We have developed new methods to synthesize 18F-pretomanid (chemically identical to the antibiotic) and performed cross-species positron emission tomography (PET) imaging to noninvasively measure pretomanid concentration-time profiles. Dynamic PET in mouse and rabbit models of TB meningitis demonstrates excellent CNS penetration of pretomanid but cerebrospinal fluid (CSF) levels does not correlate with those in the brain parenchyma. The bactericidal activity of the BPaL regimen in the mouse model of TB meningitis is substantially inferior to the standard TB regimen, likely due to restricted penetration of bedaquiline and linezolid into the brain parenchyma. Finally, first-in-human dynamic 18F-pretomanid PET in six healthy volunteers demonstrates excellent CNS penetration of pretomanid, with significantly higher levels in the brain parenchyma than in CSF. These data have important implications for developing new antibiotic treatments for TB meningitis.

DOI: 10.1038/s41467-022-35730-3
PMCID: PMC9800570
PMID: 36581633 [Indexed for MEDLINE]

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

27. **Drug resistance patterns and dynamics of tuberculosis in Zhejiang Province, China: Results from five periodic longitudinal surveys.**

Front Public Health. 2022 Nov 29;10:1047659. doi: 10.3389/fpubh.2022.1047659. eCollection 2022.

Zhou L(1), Wu B(1), Huang F(2), Liu Z(1), Wang F(1), Zhang M(1), Chen B(1), Chen S(1), Wang X(1), Zhao Y(2).

BACKGROUND: As one of the high multi-drug resistance tuberculosis countries, it is critical for China to understand patterns of drug resistance to better formulate effective treatment regimens.
METHODS: The anti-TB Drug resistance surveillance has been conducted in Zheijang Province in years 1999, 2004, 2008, 2013, and 2018 respectively. We compared the

prevalence of DR-TB from the latest survey with that of the previous four surveys in terms of all four first-line anti-TB drugs. We also examined the prevalence of rifampin-resistant TB (RR-TB) between the last two surveys and routine surveillance data.
RESULTS: Among 996 patients surveyed in 2018, the prevalence of RR-TB in new and previously treated TB cases was 2.5 and 4.3%, respectively. The prevalence of RR-TB among previously treated cases was much higher than for new cases in the four surveys from 1999 to 2013, while there was no significant difference between these groups in the 2018 survey. The percentage of TB cases resistant to fluoroquinolones in new patients was 3.8%. The prevalence of non-tuberculous mycobacteria increased over time; the prevalence of RR-TB among new cases slowly decreased. The prevalence of RR-TB in both new and previously treated TB cases from the latest two surveys was consistent with routine surveillance data.
CONCLUSIONS: This consistency between routine surveillance and periodic surveys for TB cases implies that with universal testing in Zhejiang Province, data from routine surveillance could be used instead of periodic surveys to improve access to timely and appropriate treatment for DR-TB. Levels of resistance were lower than whole-country and global estimates, further indicating the value of universal drug susceptibility testing.

DOI: 10.3389/fpubh.2022.1047659
PMCID: PMC9745021
PMID: 36523585 [Indexed for MEDLINE]

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

28. **Mycobacterium tuberculosis genetic features associated with pulmonary tuberculosis severity.**

Int J Infect Dis. 2022 Dec;125:74-83. doi: 10.1016/j.ijid.2022.10.026. Epub 2022 Oct 21.

Genestet C(1), Refrégier G(2), Hodille E(3), Zein-Eddine R(4), Le Meur A(2), Hak F(2), Barbry A(3), Westeel E(5), Berland JL(5), Engelmann A(6), Verdier I(6), Lina G(7), Ader F(8), Dray S(9), Jacob L(9), Massol F(10), Venner S(9), Dumitrescu O(7); Lyon TB study group.

OBJECTIVES: Mycobacterium tuberculosis (Mtb) infections result in a wide spectrum of clinical presentations but without proven Mtb genetic determinants.

Herein, we hypothesized that the genetic features of Mtb clinical isolates, such as specific polymorphisms or microdiversity, may be linked to tuberculosis (TB) severity.
METHODS: A total of 234 patients with pulmonary TB (including 193 drug-susceptible and 14 monoresistant cases diagnosed between 2017 and 2020 and 27 multidrug-resistant cases diagnosed between 2010 and 2020) were stratified according to TB disease severity, and Mtb genetic features were explored using whole genome sequencing, including heterologous single-nucleotide polymorphism (SNP), calling to explore microdiversity. Finally, we performed a structural equation modeling analysis to relate TB severity to Mtb genetic features.
RESULTS: The clinical isolates from patients with mild TB carried mutations in genes associated with host-pathogen interaction, whereas those from patients with moderate/severe TB carried mutations associated with regulatory mechanisms. Genome-wide association study identified an SNP in the promoter of the gene coding for the virulence regulator espR, statistically associated with moderate/severe disease. Structural equation modeling and model comparisons indicated that TB severity was associated with the detection of Mtb microdiversity within clinical isolates and to the espR SNP.
CONCLUSION: Taken together, these results provide a new insight to better understand TB pathophysiology and could provide a new prognosis tool for pulmonary TB severity.

DOI: 10.1016/j.ijid.2022.10.026
PMID: 36273524 [Indexed for MEDLINE]

29. **Hepatocellular Injury in Children Treated for Rifampicin-resistant Tuberculosis: Incidence, Etiology and Outcome.**

Pediatr Infect Dis J. 2022 Dec 1;41(12):953-958. doi: 10.1097/INF.0000000000003690. Epub 2022 Sep 6.

Duvenhage J(1), Draper HR(2), Garcia-Prats AJ(2), Winckler J(2), Hesseling AC(2), Schaaf HS(2).

BACKGROUND: Hepatocellular injury has been reported commonly in adults on rifampicin-resistant and multidrug-resistant tuberculosis (RR/MDR-TB) treatment. However, there are limited data in children.
METHODS: Two pharmacokinetic studies of children (0-17 years) routinely treated for RR/MDR-TB were conducted in Cape Town, South Africa between October 2011 and February 2020. Hepatocellular injury adverse events (AEs; defined as elevated alanine aminotransferase [ALT]) were documented serially. Data were analyzed to

determine the incidence, etiology, risk factors, management and outcome of ALT elevation.
RESULTS: A total of 217 children, median age 3.6 years (interquartile range, 1.7-7.1 years) at enrollment were included. The median follow-up time was 14.0 months (interquartile range, 9.8-17.2 months). Fifty-five (25.3%) patients developed an ALT AE. Of these, 43 of 55 (78%) patients had 54 ALT AEs attributed to their RR/MDR-TB treatment. The incidence rate of ALT AEs related to RR-TB treatment was 22.4 per 100 person-years. Positive HIV status and having an elevated ALT at enrollment were associated with time to ALT AE attributed to RR/MDR-TB treatment, with P values 0.0427 and $P < 0.0001$, respectively. Hepatitis A IgM was positive in 11 of 14 (78.6%) severe (grade ≥3) cases of ALT AEs. In 8 of 14 (57%) severe ALT AEs, hepatotoxic drugs were stopped or temporarily interrupted. None had a fatal or unresolved outcome.
CONCLUSIONS: Hepatocellular injury in children on RR/MDR-TB treatment is common, although usually mild; having elevated ALT early in treatment and HIV-positive status are possible risk factors. Hepatitis A was a common etiology of severe ALT AE in children treated for RR/MDR-TB.

DOI: 10.1097/INF.0000000000003690
PMID: 36102699 [Indexed for MEDLINE]

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

30. **Strain Diversity and Gene Mutations Associated with Presumptive Multidrug-Resistant Mycobacterium tuberculosis complex Isolates in Northwest Ethiopia.**

J Glob Antimicrob Resist. 2022 Dec 2:S2213-7165(22)00257-0. doi: 10.1016/j.jgar.2022.11.012. Online ahead of print.

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

OBJECTIVES: In this study, we assessed the genetic diversity and gene mutations that confer resistance to rifampicin (RIF), isoniazid (INH), fluoroquinolone (FQ), and second-line injectable (SLI) drugs in RR/MDR-TB isolates in Northwest Ethiopia.
METHODS: Spoligotyping was used to assign isolates to TB lineages (Ls), and Hain line probe assays (LPAs) were used to detect resistance to RIF, INH, and FQs and SLIs.

RESULTS: Among 130 analyzed strains, 68.5% were rifampicin resistance (RR), and four major Mcobacterium tuberculosis complex (MTBC) lineages (L1, L3, L4, and L7) were identified with a predominance of the Euro-American L4 (72, 54.7%), while L7-genotypes were less common (3, 2.3%). Overall, the L4-T3-ETH (41, 32.0%), L3-CAS1-Delhi (29, 22.7%) and L3-CAS1-Killi (19, 14.8%) families were most common. LPA analysis showed that among rpoB mutants, 65.2% were S450L, while 87.8% of katG mutants were S315T. Only three isolates showed mutation (c-15t) at the inhA gene, and no double mutation with katG and inhA genes was found. Six strains, two each of L1, L3, and L4, were resistant to FQs having gyrA mutations (D94G, S91P), of which three isolates had additional resistance to SLI (rrs A1401G or C1402T mutations) including one isolate with low-level kanamycin (KAN) resistant.
CONCLUSION: The study showed a predominance of L4-T3-ETH, L3-CAS1-Delhi, and L3-CAS1-Killi families, with a high rate of rpoB_S450L and katG_S315T mutations, and a low proportion of gyrA and rrs mutations. L7 was less frequent in this study. Further investigations are, therefore, needed to understand L7 and other lineages with undefined mutations.

DOI: 10.1016/j.jgar.2022.11.012
PMID: 36470362

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

31. **Effectiveness and safety of bedaquiline-based, modified all-oral 9-11-month treatment regimen for rifampicin-resistant tuberculosis in Vietnam.**

Int J Infect Dis. 2023 Jan;126:148-154. doi: 10.1016/j.ijid.2022.11.007. Epub 2022 Nov 11.

Nguyen TMP(1), Le THM(2), Merle CSC(3), Pedrazzoli D(4), Nguyen NL(4), Decroo T(5), Nguyen BH(2), Hoang TTT(2), Nguyen VN(2).

OBJECTIVES: World Health Organization recommends a 7-drug 9-11-month rifampicin-resistant tuberculosis (RR-TB) short treatment regimen (STR). To reduce the pill burden, we assessed the safety and effectiveness of a 5-drug 9-11-month modified STR (mSTR).
METHODS: Prospective cohort study of an all-oral mSTR (comprising bedaquiline, levofloxacin, linezolid [LZD], clofazimine, and/or pyrazinamide) for patients with RR-TB without confirmed fluoroquinolone resistance, enrolled in Vietnam between 2020-2021.

RESULTS: A total of 108 patients were enrolled in this study. Overall, 63 of 74 (85%) achieved culture conversion at 2 months. Of 106 evaluated, 95 (90%) were successfully treated, six (6%) were lost-to-follow-up, one (1%) died, and four (4%) had treatment failure, including three with permanent regimen change owing to adverse events (AE) and one with culture reversion. Of 108, 32 (30%) patients encountered at least one AE. Of 45 AEs recorded, 13 (29%) were serious (hospitalization, life threatening, or death). The median time to AE was 3 months (IQR: 2-5). A total of 26 AEs led to regimen adaptation: either dose reduction (N = 1), drug temporary interruption (N = 19), or drug permanent discontinuation (N = 6, 4 attributed to LZD).
CONCLUSION: The high treatment success of 5-drug mSTR might replace the 7-drug regimen in routine care. AEs were frequent, but manageable in most patients. Active AEs monitoring is essential, particularly when using LZD throughout.

DOI: 10.1016/j.ijid.2022.11.007
PMCID: PMC9789925
PMID: 36372364 [Indexed for MEDLINE]

Conflict of interest statement: Declaration of Competing Interest The authors have no competing interests to declare. Disclaimer: NNL, DP and CSCM are staff members of the World Health Organization; the authors alone are responsible for the views expressed in this publication and they do not necessarily represent the decisions, policy or views of the WHO.

32. **[A meta-analysis of risk factors for multidrug-resistant tuberculosis in China].**

Zhonghua Jie He He Hu Xi Za Zhi. 2022 Dec 12;45(12):1221-1230. doi: 10.3760/cma.j.cn112147-20220501-00366.

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

Wei SS(1), Gao Q(1), Cao YX(1), Han LY(1), Du J(2), Li L(2), Li X(1).

Objective: To explore the main risk factors of multidrug-resistant tuberculosis (MDR-TB) in China and to provide evidence-based evidence for MDR-TB preventon and control. Methods: All relevant literatures were searched in thedatabases, such as Pubmed, Web of Science and CNKI, Wanfang, VIP and SinoMed from 2000 to 2021. Quality evaluation and data extraction were carried out, and then a meta-analysis was performed using Stata 16.0 software. Results: A total of 59 literatures (36 cross-sectional and 23 case-control) including 75 793 participants were included in this study, and meta-analysis results showed age

(OR=1.27, 95%CI: 1.05-1.54), education level (OR=1.29, 95%CI: 1.02-1.65), positive sputum smear (OR=2.56, 95%CI: 1.09-6.04), pulmonary cavity (OR=1.99, 95%CI: 1.57-2.52), course of disease (OR=4.25, 95%CI: 1.95-9.30), history of tuberculosis treatment (OR=6.42,95%CI:5.40-7.63), treatment interruption (OR=2.81, 95%CI: 1.50-5.29), irregular medication (OR=5.02, 95%CI: 2.95-8.54), adverse drug reactions (OR=4.27, 95%CI: 2.22-8.19), combined chronic obstructive pulmonary disease (COPD) (OR=2.21, 95%CI: 1.45-3.37), tuberculosis exposure history (OR=1.99, 95%CI: 1.36-2.91), smoking history (OR=1.35, 95%CI: 1.09-1.66) and floating population (OR=1.60, 95%CI: 1.04-2.44) were associated with the occurrence of MDR-TB. Conclusions: The high risk groups were farmer, low education level, pulmonary cavity, long course of disease, history of tuberculosis treatment, treatment interruption, irregular medication, adverse drug reaction, co-COPD, contact history of tuberculosis, smoking history, rural residence, and floating population. We should pay attention to high-risk groups, strengthen management and take effective measures such as early screening, knowledge education on tuberculosis, standardized and personalized treatment and whole-course supervision.

DOI: 10.3760/cma.j.cn112147-20220501-00366
PMID: 36480854 [Indexed for MEDLINE]

33. **Incidence and Predictors of Adverse Drug Events Among People Receiving Drug Resistant Tuberculosis Treatment in Uganda: 8-Year Retrospective Cohort Study.**

Ther Clin Risk Manag. 2022 Dec 15;18:1117-1127. doi: 10.2147/TCRM.S381800. eCollection 2022.

Nasasira M(1), Kalyango JN(1)(2), Mupere E(3), Baluku JB(4)(5).

BACKGROUND: Adverse drug events (ADEs) are regarded as the most essential therapeutic issue during management of drug-resistant tuberculosis (DR-TB) due to the long duration of therapy and concurrent use of many second-line medications. This study aimed to determine the incidence and factors associated with ADEs among patients receiving DR-TB treatment at Mulago hospital in Uganda. METHODS: A retrospective cohort study was conducted among 417 DR-TB patient records at Mulago National Referral Hospital from January 2013 to December 2020. Using the data abstraction form, data were collected on socio-demographic and clinical factors, adverse drug events and treatment follow-up time. Data were double entered in Epi data version 3.2 and later exported to Stata version 14.0 for analysis. The incidence rate of adverse drug events was computed using number of cases of ADE divided by overall patient follow-up time. Poisson regression model was used to determine the factors associated with ADEs. The predictors were considered significant at if $p< 0.05$.

RESULTS: The overall incidence was 5.56 ADEs per 100 person months (95% confidence interval (CI) 5.01, 6.15). Treatment regimens containing an aminoglycoside (incident rate ratio (IRR) 1.106, 95% CI 1.005-1.216 p=0.0391), linezolid (IRR 1.145, 95% CI 1.008-1.229 p = 0.037) or pyrazinamide (IRR 1.226, 95% CI 1.072-1.401 p = 0.003) and the treatment duration (in months) (IRR 1.005, 95% CI 1.001-1.010 p = 0.042) were associated with ADEs.
CONCLUSION: Regimens containing aminoglycosides, linezolid, or pyrazinamide and increase in treatment duration (months) were associated with an increased risk of ADEs. Clinicians should quickly adopt all oral shorter treatment regimens to obviate the need for aminoglycosides and reduce exposure duration.

DOI: 10.2147/TCRM.S381800
PMCID: PMC9762173
PMID: 36544865

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

34. **Stable sugar and sugar-free suspensions of pretomanid.**

Int J Tuberc Lung Dis. 2022 Dec 1;26(12):1112-1117. doi: 10.5588/ijtld.22.0330.

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

BACKGROUND: Pretomanid (PMD) tablets are indicated as part of a combination regimen for the treatment of adults with pulmonary extensively drug-resistant, treatment-intolerant or non-responsive multidrug-resistant TB. No commercial liquid formulation is currently available for patients unable to swallow these tablets.OBJECTIVE: To develop stable extemporaneous liquid formulations of PMD that can be stored at room temperature or 30°C for at least 4 weeks.METHODS: Crushed PMD tablets were formulated into 20 mg/mL suspensions in a simple syrup and sugar-free formulation. The PMD formulations were stored at room temperature and at 30°C for 30 days in dispensing bottles. Appearance, pH, potency and microbial counts of the suspensions were determined on Days 0, 15 and 30.RESULTS: The potency of PMD remained at 99.7-103.4% of the theoretical concentration in each formulation. The appearance, pH and microbial count did not change during the 30-day storage period. Simple syrup formulations did not require preservatives for microbial stability.CONCLUSIONS: PMD oral suspension formulations in simple syrup or in sugar-free vehicle were easily prepared by utilising commonly available equipment and ingredients and were stable for 30

days. These formulations are appropriate alternatives for patients with swallowing difficulties.

DOI: 10.5588/ijtld.22.0330
PMCID: PMC9728945
PMID: 36447311 [Indexed for MEDLINE]

35. **Pretreatment attrition and treatment initiation delay among rifampicin-resistant tuberculosis patients in Lagos, Nigeria: a retrospective cohort study.**

Trans R Soc Trop Med Hyg. 2022 Dec 2;116(12):1154-1161. doi: 10.1093/trstmh/trac054.

Adejumo OA(1)(2), Daniel O(3), Adepoju VA(4), Onoh MO(5), Sokoya OD(6), Abdur-Razzaq H(7), Moronfolu O(6), Oyadotun OM(8), Olusola-Faleye B(9).

BACKGROUND: Assessing associated factors of pretreatment attrition and treatment delays among rifampicin-resistant tuberculosis (RR-TB) patients could serve as a valuable tool to control and prevent its community spread. We assessed the factors associated with pretreatment attrition and treatment initiation delays among RR-TB patients in Lagos, Nigeria.
METHODS: A retrospective cohort study was conducted involving secondary program data of RR-TB patients diagnosed using the Xpert MTB/RIF assay and initiated on treatment between 1 January 2015 and 31 December 2017 in Lagos. Factors associated with pretreatment attrition and treatment initiation delay were determined using logistic regression.
RESULTS: Of the 606 RR-TB patients diagnosed during the review period, 135 (22.3%) had pretreatment attrition. Previously treated TB patients had a 2.4-fold greater chance of having pretreatment attrition than new RR-TB patients (adjusted odds ratio 2.4 [95% confidence interval 1.2-5.0]). The median time to treatment initiation was 29 d (interquartile range [IQR] 18-49). It was longer for new RR-TB patients (49 d [IQR 36-59]) than previously treated TB patients (28 d [IQR 17-44]). A total of 47% had long treatment delays. Being newly diagnosed with RR-TB was associated with long treatment delays.
CONCLUSIONS: The pretreatment attrition rate and proportion of RR-TB patients with treatment delays were high. Pragmatic approaches to address the high pretreatment attrition and treatment delays in Lagos, Nigeria, are urgently needed.

DOI: 10.1093/trstmh/trac054

PMID: 35710310 [Indexed for MEDLINE]

36. **A 24-Week, All-Oral Regimen for Rifampin-Resistant Tuberculosis.**

N Engl J Med. 2022 Dec 22;387(25):2331-2343. doi: 10.1056/NEJMoa2117166.

Nyang'wa BT(1), Berry C(1), Kazounis E(1), Motta I(1), Parpieva N(1), Tigay Z(1), Solodovnikova V(1), Liverko I(1), Moodliar R(1), Dodd M(1), Ngubane N(1), Rassool M(1), McHugh TD(1), Spigelman M(1), Moore DAJ(1), Ritmeijer K(1), du Cros P(1), Fielding K(1); TB-PRACTECAL Study Collaborators.

Comment in
N Engl J Med. 2022 Dec 22;387(25):2380-2381.

BACKGROUND: In patients with rifampin-resistant tuberculosis, all-oral treatment regimens that are more effective, shorter, and have a more acceptable side-effect profile than current regimens are needed.
METHODS: We conducted an open-label, phase 2-3, multicenter, randomized, controlled, noninferiority trial to evaluate the efficacy and safety of three 24-week, all-oral regimens for the treatment of rifampin-resistant tuberculosis. Patients in Belarus, South Africa, and Uzbekistan who were 15 years of age or older and had rifampin-resistant pulmonary tuberculosis were enrolled. In stage 2 of the trial, a 24-week regimen of bedaquiline, pretomanid, linezolid, and moxifloxacin (BPaLM) was compared with a 9-to-20-month standard-care regimen. The primary outcome was an unfavorable status (a composite of death, treatment failure, treatment discontinuation, loss to follow-up, or recurrence of tuberculosis) at 72 weeks after randomization. The noninferiority margin was 12 percentage points.
RESULTS: Recruitment was terminated early. Of 301 patients in stage 2 of the trial, 145, 128, and 90 patients were evaluable in the intention-to-treat, modified intention-to-treat, and per-protocol populations, respectively. In the modified intention-to-treat analysis, 11% of the patients in the BPaLM group and 48% of those in the standard-care group had a primary-outcome event (risk difference, -37 percentage points; 96.6% confidence interval [CI], -53 to -22). In the per-protocol analysis, 4% of the patients in the BPaLM group and 12% of those in the standard-care group had a primary-outcome event (risk difference, -9 percentage points; 96.6% CI, -22 to 4). In the as-treated population, the incidence of adverse events of grade 3 or higher or serious adverse events was lower in the BPaLM group than in the standard-care group (19% vs. 59%).
CONCLUSIONS: In patients with rifampin-resistant pulmonary tuberculosis, a 24-week, all-oral regimen was noninferior to the accepted standard-care treatment, and it had a better safety profile. (Funded by Médecins sans Frontières; TB-PRACTECAL ClinicalTrials.gov number, NCT02589782.).

DOI: 10.1056/NEJMoa2117166
PMID: 36546625 [Indexed for MEDLINE]

37. **Adjunctive Zoledronate + IL-2 administrations enhance anti-tuberculosis Vγ2Vδ2 T-effector populations, and improve treatment outcome of multidrug-resistant tuberculosis(1).**

Emerg Microbes Infect. 2022 Dec;11(1):1790-1805. doi: 10.1080/22221751.2022.2095930.

Shen H(1), Yang E(1)(2), Guo M(3), Yang R(1), Huang G(1), Peng Y(1), Sha W(1), Wang F(4), Shen L(2).

Multidrug-resistant tuberculosis (MDR-TB) is a refractory disease with high mortality rate due to no or few choices of antibiotics. Adjunctive immunotherapy may help improve treatment outcome of MDR-TB. Our decade-long studies demonstrated that phosphoantigen-specific Vγ2Vδ2 T cells play protective roles in immunity against TB. Here, we hypothesized that enhancing protective Vγ2Vδ2 T-effector cells could improve treatment outcome of MDR-TB. To address this, we employed clinically approved drugs Zoledronate (ZOL) and IL-2 to induce anti-TB Vγ2Vδ2 T-effector cells as adjunctive immunotherapy against MDR-TB infection of macaques. We found that adjunctive ZOL/IL-2 administrations during TB drugs treatment of MDR-TB-infected macaques significantly expanded Vγ2Vδ2 T cells and enhanced/sustained Vγ2Vδ2 T-effector subpopulation producing anti-TB cytokines until week 21. ZOL/IL-2 administrations, while expanding Vγ2Vδ2 T cells, significantly increased/sustained numbers of circulating CD4+ Th1 and CD8+ Th1-like effector populations, with some γδ T- or αβ T-effector populations trafficking to airway at week 3 until week 19 or 21 after MDR-TB infection. Adjunctive ZOL/IL-2 administrations after MDR-TB infection led to lower bacterial burdens in lungs than TB drugs alone, IL-2 alone or saline controls, and resulted in milder MDR-TB pathology/lesions. Thus, adjunctive Zoledronate + IL-2 administrations can enhance anti-TB Vγ2Vδ2 T- and αβ T-effector populations, and improve treatment outcome of MDR-TB.

DOI: 10.1080/22221751.2022.2095930
PMCID: PMC9310823
PMID: 35765887 [Indexed for MEDLINE]

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

38. **Sputum smear conversion and treatment outcomes among drug-resistant pulmonary tuberculosis patients in eastern Ethiopia: A 9-years data analysis.**

Front Med (Lausanne). 2022 Dec 1;9:1007757. doi: 10.3389/fmed.2022.1007757. eCollection 2022.

Gamachu M(1)(2), Deressa A(3), Birhanu A(1), Ayana GM(3), Raru TB(3), Negash B(3), Merga BT(3), Alemu A(3), Ahmed F(3), Mohammed A(2), Abdulahi IM(3), Regassa LD(3).

BACKGROUND: Drug-resistant tuberculosis (DR-TB) has become a public health problem throughout the world and about one-third of deaths were attributed to DR-TB from antimicrobial resistance which contributes to 10% of all TB deaths. Sub-Saharan Africa, particularly Ethiopia accounts for a significant number of TB cases. However, the scanty evidence on DR-TB contributing factors could affect the level of this deadly case tackling program. Therefore, this study aimed to assess the factors affecting sputum smear conversion and treatment outcomes among patients with DR-TB in Health facilities in Eastern Ethiopia.
METHODS AND MATERIALS: A cross-sectional study design was employed from 10 October to 10 November 2021, in the health facilities providing DR-TB services in Harari Region and Dire Dawa city administration. The medical records of 273 DR-TB patients from 10 January 2013 to 27 December 2021, were reviewed using structured checklists. Data were entered into Epidata 3.1 version and exported to STATA 14 version for analysis. The outcome variables were Initial Sputum conversion (converted vs. not-converted) and treatment outcome (Unfavorable vs. Favorable). Sputum examination was performed using both Acid-fast bacillus (AFB) smear microscopy and Löwenstein-Jensen (LJ) culture technique. A binary logistic regression analysis was used to assess the association of independent variables with the first month sputum smear conversion, while a conditional logistic regression model was used to assess the association of treatment outcome with explanatory variables. The associations were reported using adjusted odds ratios (AORs) at a 95% confidence interval.
RESULTS: A total of 273 DR-TB patients were included in this study. The unfavorable DR-TB treatment outcome was significantly associated with the history of chewing khat (AOR = 4.38, 95% CI = 1.62, 11.84), having bilateral lung cavity on baseline chest X-ray (AOR = 12.08, 95% CI = 1.80, 2.57), having greater than 2+ smear result at baseline (AOR = 3.79, 95% CI = 1.35, 10.59), and poor adherence (AOR = 2.9, 95% CI = 1.28, 6.82). The sputum smear non-conversion at first month was significantly associated with being Human Immune Virus (HIV)-negative (AOR = 0.37, 0.17, 0.82), having low baseline BMI (AOR = 0.54, 95% CI = 0.29, 0.97), baseline culture > 2++ (AOR = 0.15, 95% CI = 0.05, 0.49) and having greater than 2+ sputum smear result (AOR = 0.09, 95% CI = 0.012,

0.67). Patients with normal chest X-ray at baseline had 3.8 times higher chance of sputum smear conversion on first month (AOR = 3.77, 1.11, 12.77). CONCLUSION: The overall initial sputum smear conversion and the treatment success rate among DR-TB patients were 52.75 and 66.30%, respectively. The Baseline underweight, HIV-negative, baseline smear > 2+, baseline culture > 2++, and clear lung on baseline X-ray were associated with smear conversion and history of khat chewing, bilateral lung cavity at baseline, having greater than 2+ smear results at baseline, and patients with poor treatment adherence had hostile treatment outcomes. So, strengthening and implementing nutrition assessment and patient counseling during directly observed therapies (DOTs) service and drug compliance could result in early sputum conversion and better treatment outcomes. DR-TB patients with high bacterial load and abnormal lungs on radiologic examination at baseline could need special attention during their course of treatment.

DOI: 10.3389/fmed.2022.1007757
PMCID: PMC9751062
PMID: 36530886

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

39. **Effect modification of greenness on PM(2.5) associated all-cause mortality in a multidrug-resistant tuberculosis cohort.**

Thorax. 2022 Dec;77(12):1202-1209. doi: 10.1136/thoraxjnl-2020-216819. Epub 2021 Dec 7.

Ge E(1), Gao J(1), Wei X(1), Ren Z(2), Wei J(3), Liu X(4), Wang X(5), Zhong J(5), Lu J(6), Tian X(6), Fei F(5), Chen B(5), Wang X(6), Peng Y(7), Luo M(8), Lei J(9).

RATIONALE: Evidence for the association between fine particulate matter (PM2.5) and mortality among patients with tuberculosis (TB) is limited. Whether greenness protects air pollution-related mortality among patients with multidrug-resistant tuberculosis (MDR-TB) is completely unknown. METHODS: 2305 patients reported in Zhejiang and Ningxia were followed up from MDR-TB diagnosis until death, loss to follow-up or end of the study (31 December 2019), with an average follow-up of 1724 days per patient. 16-day averages of

contemporaneous Normalised Difference Vegetation Index (NDVI) in the 500 m buffer of patient's residence, annual average PM2.5 and estimated oxidant capacity Ox were assigned to patients regarding their geocoded home addresses. Cox proportional hazards regression models were used to estimate HRs per 10 μ g/m3 exposure to PM2.5 and all-cause mortality among the cohort and individuals across the three tertiles, adjusting for potential covariates.
RESULTS: HRs of 1.702 (95% CI 1.680 to 1.725) and 1.169 (1.162 to 1.175) were observed for PM2.5 associated with mortality for the full cohort and individuals with the greatest tertile of NDVI. Exposures to PM2.5 were stronger in association with mortality for younger patients (HR 2.434 (2.432 to 2.435)), female (2.209 (1.874 to 2.845)), patients in rural (1.780 (1.731 to 1.829)) and from Ningxia (1.221 (1.078 to 1.385)). Cumulative exposures increased the HRs of PM2.5-related mortality, while greater greenness flattened the risk with HRs reduced in 0.188-0.194 on average.
CONCLUSIONS: Individuals with MDR-TB could benefit from greenness by having attenuated associations between PM2.5 and mortality. Improving greener space and air quality may contribute to lower the risk of mortality from TB/MDR-TB and other diseases.

DOI: 10.1136/thoraxjnl-2020-216819
PMID: 34876501 [Indexed for MEDLINE]

Conflict of interest statement: Competing interests: None declared.

40. **High clustering rate and genotypic drug-susceptibility screening for the newly recommended anti-tuberculosis drugs among global extensively drug-resistant Mycobacterium tuberculosis isolates.**

Emerg Microbes Infect. 2022 Dec;11(1):1857-1866. doi: 10.1080/22221751.2022.2099304.

Trisakul K(1)(2), Nonghanphithak D(1)(2), Chaiyachat P(1)(2), Kaewprasert O(1)(2), Sakmongkoljit K(3), Reechaipichitkul W(1)(2), Chaiprasert A(4), Blair D(5), Clark TG(6), Faksri K(1)(2).

Multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) make TB difficult to control. Global susceptibility data for six newly recommended anti-TB drugs against M/XDR-TB are still limited. Using publicly available whole-genome sequences, we determined the proportion of 513 phenotypically XDR-TB isolates that carried mutations associated with

resistance against these drugs (bedaquiline, clofazimine, linezolid, delamanid, pretomanid and cycloserine). Mutations of Rv0678 and Rv1979c were detected in 69/513 isolates (13.5%) for bedaquiline resistance and 79/513 isolates (15.4%) for clofazimine resistance with additional mmpL5 mutations. Mutations conferring resistance to delamanid were detected in fbiB and ddn genes for 11/513 isolates (2.1%). For pretomanid, a mutation was detected in the ddn gene for 3/513 isolates (0.6%). Nineteen mutations of pykA, cycA, ald, and alr genes, conferring resistance to cycloserine, were found in 153/513 isolates (29.8%). No known mutations associated with linezolid resistance were detected. Cluster analysis showed that 408/513 isolates fell within 99 clusters and that 354 of these isolates were possible primary drug-resistant TB (292 XDR-TB, 57 pre-XDR-TB and 5 MDR-TB). Clonal transmission of primary XDR isolates might contribute significantly to the high prevalence of DR-TB globally.

DOI: 10.1080/22221751.2022.2099304
PMCID: PMC9336503
PMID: 35792049 [Indexed for MEDLINE]

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

41. **A five-year review of prevalence and treatment outcomes of pre-extensively drug-resistant plus additional drug-resistant tuberculosis in the Henan Provincial Tuberculosis Clinical Medicine Research Centre.**

J Glob Antimicrob Resist. 2022 Dec;31:328-336. doi: 10.1016/j.jgar.2022.09.010. Epub 2022 Oct 6.

Li Z(1), Liu F(2), Chen H(3), Han Y(3), You Y(2), Xie Y(2), Zhao Y(3), Tan J(3), Guo X(3), Cheng Y(3), Wang Y(3), Li J(3), Cheng M(3), Xia S(3), Niu X(3), Wei L(3), Wang W(4).

OBJECTIVES: This study investigated the prevalence and significant clinical outcomes of pre-extensively drug-resistant plus additional drug-resistant tuberculosis (pre-XDR-plus) in Henan Provincial Chest Hospital between 2017 and 2021.
METHODS: We analysed and summarized the drug sensitivity test (DST) results of clinical Mycobacterium tuberculosis (MTB) strains in TB patients seeking care in the Tuberculosis Clinical Medical Research Centre of Henan Province between 2017 and 2021. Medical records of pre-extensively drug-resistant plus additional drug-resistant TB patients were statistically analysed, including demographic characteristics, regimens, and outcomes.
RESULTS: Of the 3689 Mycobacterium tuberculosis strains, 639 (17.32%), 353

(9.56%), and 109 (2.95%), multidrug-resistant tuberculosis (MDR-TB), pre-extensively drug-resistant tuberculosis (pre-XDR), and pre-XDR-plus, respectively. The proportion of MDR decreased from 19.1% in 2017 to 17.5% in 2021 ($\chi2$ = 0.686, P = 0.407), the proportion of pre-XDR from 11.4% in 2017 to 9.0% in 2021 ($\chi2$ = 2.39, P = 0.122), and pre-XDR-plus from 4.7% in 2017 to 1.8% in 2020, with the declining trend was significant ($\chi2$ = 9.348, P = 0.002). The most commonly used anti-TB drugs were pyrazinamide (PZA, 37/46, 80.43%) and cycloserine (CS, 32/46, 69.57%), followed by linezolid (LZD, 25/46, 54.35%), protionamide (TH, 25/46, 54.35%), and para-aminosalicylic acid (PAS, 23/46, 50.00%). Patients receiving the LZD regimen were 5 times more likely to have a favourable outcome than those not receiving LZD (OR = 6.421, 95% CI 2.101-19.625, P = 0.001). Patients receiving a regimen containing CS were 4 times more likely to have a favourable outcome compared to those not taking CS (OR = 5.444, 95% CI 1.650-17.926, P = 0.005).
CONCLUSIONS: Our data suggest that the population of pre-XDR-plus had significantly decreased over the past five years in the Henan Provincial Chest Hospital. The COVID-19 and flood disaster affect TB patients' selection of medical services. In addition, the pre-XDR-plus patients whose regimens contain LZD or CS were more likely to have favourable outcomes.

DOI: 10.1016/j.jgar.2022.09.010
PMID: 36210030 [Indexed for MEDLINE]

42. **Spontaneous Mutational Patterns and Novel Mutations for Delamanid Resistance in Mycobacterium tuberculosis.**

Antimicrob Agents Chemother. 2022 Dec 20;66(12):e0053122. doi: 10.1128/aac.00531-22. Epub 2022 Nov 30.

Liu Y(#)(1), Shi J(#)(2), Li L(#)(3), Wu T(4), Chu P(1), Pang Y(3), Guo Y(1), Gao M(2), Lu J(1).

Delamanid (DLM) and pretomanid (PTM) are recent additions to the anti-tuberculosis (TB) drug armamentarium, and they offer more effective options for drug-resistant TB treatment. In particular, DLM is included in Group C, which is recommended for use in longer multidrug-resistant (MDR)-TB regimens. Previous studies have shown that resistance to DLM/PTM is caused by mutations in the ddn, fgd1, fbiA, fbiB, fbiC, and fbiD genes, which are related to the F420-dependent bioactivation pathway. Herein, we conduct in vitro selection of DLM-resistant strains using clinical Mycobacterium tuberculosis (MTB) isolates with various drug resistance profiles. The spontaneous resistance frequency of

drug-susceptible (DS) MTB (1.14 × 10-6 to 1.04 × 10-4) to DLM was similar to that of H37Rv (8.88 × 10-6 to 9.96 × 10-6) but higher than those of multidrug-resistant MTB (2.03 × 10-7 to 3.18 × 10-6) and extensively drug-resistant (XDR) MTB (4.67 × 10-8 to 3.60 × 10-6). Of the 100 independently selected DLM-resistant MTB mutants, 65% harbored mutations in genes associated with either DLM prodrug activation (ddn, 39.73%; fgd1, 16.44%) or the F420 biosynthetic pathway (fbiA, 16.44%; fbiB, 5.48%; fbiC, 21.92%). Of the 45 mutations we identified, 38 were not previously reported. A structure analysis revealed that several point mutations affected the ligand binding or structural stability of enzymes related to DLM resistance, which would block the enzyme activity required for prodrug activation. Our results elucidate the in vitro spontaneous DLM-resistance patterns of different clinical strains, which could improve the understanding of the causes of DLM resistance in clinical strains and of the effects on drug resistance of different mutations in genes that are related to the DLM activation pathway.

DOI: 10.1128/aac.00531-22
PMCID: PMC9765178
PMID: 36448833 [Indexed for MEDLINE]

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

43. **Rapid and Ultrasensitive Approach for the Simultaneous Detection of Multilocus Mutations to Distinguish Rifampicin-Resistant Mycobacterium tuberculosis.**

Anal Chem. 2022 Dec 20;94(50):17653-17661. doi: 10.1021/acs.analchem.2c04399. Epub 2022 Dec 6.

Cao G(1), Qiu Y(1), Long K(1), Ma Y(2), Luo H(2), Yang M(1), Hou J(3), Huo D(1)(2), Hou C(1)(2).

The untested empirical medications exacerbated the development of multidrug-resistant Mycobacterium tuberculosis (MDR-TB). Here, we develop a rapid and specific method based on loop-mediated isothermal amplification and duplex-specific nuclease for distinguishing rifampicin-resistant M. tuberculosis. Three probes were designed for the codons 516, 526, and 531 on the RNA polymerase β-subunit (rpoB) gene. These three sites accounted for more than 90% of the total mutations of the ropB gene in the rifampicin-resistant strain. The approach can perform simultaneous and sensitive detection of three mutant sites with the actual detection limit as 10 aM of DNA and 62.5 cfu·mL-1 of bacteria in 67 min under isothermal conditions. Moreover, the positive mode of the approach for MDR-TB can not only deal with the randomness and diversity of mutations but also provide an easier way for medical staff to read the results.

Therefore, it is a particularly valuable method to handle major and urgent MDR-TB diagnostics.

DOI: 10.1021/acs.analchem.2c04399
PMID: 36473113 [Indexed for MEDLINE]

44. **Nosiheptide Harbors Potent In Vitro and Intracellular Inhbitory Activities against Mycobacterium tuberculosis.**

Microbiol Spectr. 2022 Dec 21;10(6):e0144422. doi: 10.1128/spectrum.01444-22. Epub 2022 Oct 12.

Yu X(1), Zhu R(1), Geng Z(2), Kong Y(1), Wang F(1), Dong L(1), Zhao L(1), Xue Y(1), Ma X(3), Huang H(1).

Multidrug-resistant tuberculosis (MDR-TB) is often associated with poor clinical outcomes. In this study, we evaluated the potential of nosiheptide (NOS) as a new drug candidate for treating Mycobacterium tuberculosis infections, including MDR-TB. The antimicrobial susceptibility testing was performed to determine the MICs of NOS against 18 reference strains of slowly growing mycobacteria (SGM) and 128 clinical isolates of M. tuberculosis. The postantibiotic effects (PAE) and interaction with other antituberculosis drugs of NOS were also evaluated using M. tuberculosis H37Rv. Fifteen out of the 18 tested reference strains of SGM had MICs far below 1 μg/mL. From the 128 M. tuberculosis clinical isolates, the MIC50 and MIC90 were 0.25 μg/mL and 1 μg/mL, respectively; the tentative epidemiological cutoff (ECOFF) was defined at 1 μg/mL. Furthermore, a Lys89Thr mutation was found in one M. tuberculosis isolate with a MIC of NOS >8 μg/mL. After 24 h of incubation, NOS at 1 μg/mL inhibited 25.79 ± 1.22% of intracellular bacterial growth, which was comparable with the inhibitory rate of 25.71 ± 3.67% achieved by rifampin at 2 μg/mL. Compared to rifampicin and isoniazid (INH), NOS had a much longer PAE, i.e., a value of about 16 days. In addition, a partial synergy between NOS and INH was observed. NOS has potent inhibitory activities against M. tuberculosis in vitro as well as in macrophages. Furthermore, the long PAE and partial synergistic effect with INH, in addition to the added safety of long-term use as a feed additive in husbandry, provide support for NOS being a promising drug candidate for tuberculosis treatment. IMPORTANCE This study is aimed at chemotherapy for MDR-TB, mainly to explore the anti-TB activity of the existing chemotherapeutic reagent. We found that NOS has potent inhibitory activities against M. tuberculosis in vitro regardless of the drug-resistant profile. Furthermore, NOS also showed the long PAE and partial synergistic effect with INH and is nontoxic, providing support for its promise as a drug candidate for drug-resistant tuberculosis treatment.

DOI: 10.1128/spectrum.01444-22
PMCID: PMC9769715
PMID: 36222690 [Indexed for MEDLINE]

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

45. **Optimized LC-MS/MS quantification of tuberculosis drug candidate macozinone (PBTZ169), its dearomatized Meisenheimer Complex and other metabolites, in human plasma and urine.**

J Chromatogr B Analyt Technol Biomed Life Sci. 2022 Dec 9;1215:123555. doi: 10.1016/j.jchromb.2022.123555. Online ahead of print.

Desfontaine V(1), Guinchard S(1), Marques S(1), Vocat A(2), Moulfi F(3), Versace F(1), Huser-Pitteloud J(1), Ivanyuk A(1), Bardinet C(1), Makarov V(4), Ryabova O(5), André P(1), Prod'Hom S(1), Chtioui H(1), Buclin T(6), Cole ST(7), Decosterd L(8).

Tuberculosis, and especially multidrug-resistant tuberculosis (MDR-TB), is a major global health threat which emphasizes the need to develop new agents to improve and shorten treatment of this difficult-to-manage infectious disease. Among the new agents, macozinone (PBTZ169) is one of the most promising candidates, showing extraordinary potency in vitro and in murine models against drug-susceptible and drug-resistant Mycobacterium tuberculosis. A previous analytical method using liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) was developed by our group to support phase I clinical trials of PBTZ169. These plasma sample analyses revealed the presence of several additional metabolites among which the most prominent was H2PBTZ, a reduced species obtained by dearomatization of macozinone, one of the first examples of Meisenheimer Complex (MC) metabolites identified in mammals. Identification of these new metabolites required the optimization of our original method for enhancing the selectivity between isobaric metabolites as well as for ensuring optimal stability for H2PBTZ analyses. Sample preparation methods were also developed for plasma and urine, followed by extensive quantitative validation in accordance with international bioanalytical method recommendations, which include selectivity, linearity, qualitative and quantitative matrix effect, trueness, precision and the establishment of accuracy profiles using β -expectation tolerance intervals for known and newer analytes. The newly optimized methods have been applied in a subsequent Phase Ib clinical trial conducted in our University Hospital with healthy subjects. H2PBTZ was found to be the most abundant species circulating in plasma, underscoring the importance of measuring accurately and precisely this unprecedented metabolite. Low

concentrations were found in urine for all monitored analytes, suggesting extensive metabolism before renal excretion.

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PMID: 36563654

Conflict of interest statement: Declaration of Competing Interest The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Stewart Cole reports financial support was provided by The Bill & Melinda Gates Foundation (INV-010544). Laurent Decosterd reports financial support was provided by Swiss National Science Foundation. Stewart Cole has patent #WO2012066518A1 (US20130245007A1) issued to licensee. Vadim Makarov has patent #WO2012066518A1 (US20130245007A1) issued to licensse. N.A.

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

J Glob Antimicrob Resist. 2022 Dec;31:256-262. doi: 10.1016/j.jgar.2022.10.004. Epub 2022 Oct 20.

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

OBJECTIVES: Whole-genome sequencing (WGS) of Mycobacterium tuberculosis (MTB), proven to be a better alternative when compared with the combined sensitivity and specificity of all other modalities for diagnosis of tuberculosis (TB), aids epidemiological surveillance investigations by combining the current research with diagnostics. This study was conducted to identify and resolve operational challenges in performing WGS-based drug resistance testing (DRT) for MTB in a TB culture and drug susceptibility testing (DST) laboratory. Three critical, non-redundant steps for WGS-based DRT were tested: viz. DNA extraction, high-throughput paired-end next-generation sequencing (NGS), and genomic analysis pipeline for automated reporting of WGS-based DRT.
METHODS: DNA was extracted from 100 liquid culture isolates on a mycobacterial growth indicator tube (MGIT) using DNEASY Ultraclean Microbial Kit (Qiagen, USA) as per the manufacturer's instructions. Illumina paired-end sequencing was performed. All analysis steps were automated using custom python scripts, requiring no intervention. Variant calling was performed as per the World Health Organization (WHO) technical guide.
RESULTS: The number of cultures resistant to rifampicin, isoniazid, pyrazinamide, ethambutol, and streptomycin was 89, 88, 35, 67, and 73,

respectively. Resistance to amikacin, kanamycin, and capreomycin was found in 15, 17, and 15 cultures, respectively. Seventy cultures were resistant to fluoroquinolones, four were resistant to ethionamide, and 12 were resistant to linezolid. Six cultures were resistant to only one of the 18 drugs tested. Seventy-five cultures were resistant to more than three anti-TB drugs. One culture was resistant to 13 of the 18 anti-TB drugs tested for this study. The maximum number of variants were observed in the rpoB gene (n = 93, 93%), wherein the Ser450Leu was the predominant mutation (n = 68, 73%). Ser315Thr was the most common variant (n = 86, 97%) that encoded resistance to isoniazid. The Lys43Arg variant encodes resistance to streptomycin and was the third most predominant variant (n = 65, 89%). In addition to the high levels of resistance observed in the dataset, we also observed a high proportion of Beijing strains (n = 63, 63%).
CONCLUSION: Compared with results from routine diagnostics based on the 'Guidelines on Programmatic Management of Drug-Resistant TB (PMDT) in India', none of the samples had DST available for all 18 drugs. This represents a gap in PMDT guidelines. The WGS-DRT must be considered as the primary DST method after a sample is flagged rifampicin-resistant by cartridge-based nucleic acid amplification testing (CBNAAT). With several research studies currently underway globally to identify novel variants associated with drug resistance and classifiy their minimum inhibitory coefficients, WGS-DRT presents a scalable technology that updates analytical pipelines, relegating the need for changing microbiological protocols.

DOI: 10.1016/j.jgar.2022.10.004
PMID: 36272707 [Indexed for MEDLINE]

47. **Factors affecting time to treatment initiation after diagnosis for multidrug-resistant/rifampicin-resistant tuberculosis patients: A mixed-methods study in Jakarta, Indonesia.**

Trop Med Int Health. 2022 Dec 7. doi: 10.1111/tmi.13838. Online ahead of print.

Silitonga P(1), Jiang W(2), Wyatt S(3), Burhan E(4), Kes EFM(5), Long Q(1).

OBJECTIVE: To investigate the time to treatment initiation (TTI) for multidrug-resistant/rifampicin-resistant tuberculosis (MDR/RR-TB) patients after diagnosis in Indonesia and biological, psychological and social factors associated with the time interval.
METHODS: This study was conducted in Persahabatan Hospital, Jakarta using a mixed-methods approach. Registry data and medical records of MDR/RR-TB patients

were collected and matched (hospital dataset), and linked with psychosocial assessment results (linked dataset). Descriptive analysis was conducted to understand patient characteristics and the distribution of TTI after RR-TB diagnosis by GeneXpert. Generalised linear regression was used to analyse factors associated with delay duration, and logistic regression to explore factors associated with the delay longer than the median duration for both datasets (basic vs. extended model). In-depth interviews were conducted with patients and healthcare workers to understand the procedure of treatment initiation and how different factors led to delay.
RESULTS: The hospital dataset included 275 patient-matched cases, and 188 were further linked with psychosocial assessment results. The median time interval was 24 days [interquartile range (IQR) 23.5] and 26 days (IQR 21.25), respectively. Regression analysis showed that in the extended model, comorbidities (exp [coefficient]= 1.93), unemployment (exp [coefficient] = 1.80) and poor knowledge of MDR/RR-TB (exp (coefficient) = 1.67) seemed to have the strongest effects on prolonging the time interval ($p < 0.05$). Unsuccessful TB treatment history was the only factor that significantly increased the risk of delay longer than the median duration ($p < 0.05$) in the basic model, while none of the factors were significant in the extended model. The qualitative study identified provider-side factors (centralised service provision and insufficient human resources) and patient-side factors (physical weakness, psychological stress and financial concern) associated with treatment delay.
CONCLUSION: MDR/RR-TB patients in Persahabatan Hospital, Jakarta, Indonesia waited around 25 days for treatment initiation after RR-TB diagnosis. Health system solutions are needed to address challenges facing both MDR/RR-TB patients and healthcare providers to reduce delay in treatment initiation.

DOI: 10.1111/tmi.13838
PMID: 36477995

48. **Impact of molecular diagnostic tests on diagnostic and treatment delays in tuberculosis: a systematic review and meta-analysis.**

BMC Infect Dis. 2022 Dec 14;22(1):940. doi: 10.1186/s12879-022-07855-9.

Lee JH(#)(1), Garg T(#)(2), Lee J(3), McGrath S(4), Rosman L(5), Schumacher SG(6), Benedetti A(7)(8), Qin ZZ(9), Gore G(10), Pai M(11), Sohn H(12).

BACKGROUND: Countries with high TB burden have expanded access to molecular diagnostic tests. However, their impact on reducing delays in TB diagnosis and treatment has not been assessed. Our primary aim was to summarize the

quantitative evidence on the impact of nucleic acid amplification tests (NAAT) on diagnostic and treatment delays compared to that of the standard of care for drug-sensitive and drug-resistant tuberculosis (DS-TB and DR-TB).
METHODS: We searched MEDLINE, EMBASE, Web of Science, and the Global Health databases (from their inception to October 12, 2020) and extracted time delay data for each test. We then analysed the diagnostic and treatment initiation delay separately for DS-TB and DR-TB by comparing smear vs Xpert for DS-TB and culture drug sensitivity testing (DST) vs line probe assay (LPA) for DR-TB. We conducted random effects meta-analyses of differences of the medians to quantify the difference in diagnostic and treatment initiation delay, and we investigated heterogeneity in effect estimates based on the period the test was used in, empiric treatment rate, HIV prevalence, healthcare level, and study design. We also evaluated methodological differences in assessing time delays.
RESULTS: A total of 45 studies were included in this review (DS = 26; DR = 20). We found considerable heterogeneity in the definition and reporting of time delays across the studies. For DS-TB, the use of Xpert reduced diagnostic delay by 1.79 days (95% CI - 0.27 to 3.85) and treatment initiation delay by 2.55 days (95% CI 0.54-4.56) in comparison to sputum microscopy. For DR-TB, use of LPAs reduced diagnostic delay by 40.09 days (95% CI 26.82-53.37) and treatment initiation delay by 45.32 days (95% CI 30.27-60.37) in comparison to any culture DST methods.
CONCLUSIONS: Our findings indicate that the use of World Health Organization recommended diagnostics for TB reduced delays in diagnosing and initiating TB treatment. Future studies evaluating performance and impact of diagnostics should consider reporting time delay estimates based on the standardized reporting framework.

DOI: 10.1186/s12879-022-07855-9
PMCID: PMC9748908
PMID: 36517736 [Indexed for MEDLINE]

Conflict of interest statement: SS reports working for Foundation for Innovative New Diagnostics (FIND).

49. **Transporter and metabolizer gene polymorphisms affect fluoroquinolone pharmacokinetic parameters.**

Front Pharmacol. 2022 Dec 12;13:1063413. doi: 10.3389/fphar.2022.1063413. eCollection 2022.

Annisa N(1)(2), Barliana MI(1)(3), Santoso P(4), Ruslami R(5).

Tuberculosis (TB) is an infectious disease that occurs globally. Treatment of TB has been hindered by problems with multidrug-resistant strains (MDR-TB). Fluoroquinolones are one of the main drugs used for the treatment of MDR-TB. The success of therapy can be influenced by genetic factors and their impact on pharmacokinetic parameters. This review was conducted by searching the PubMed database with keywords polymorphism and fluoroquinolones. The presence of gene polymorphisms, including UGT1A1, UGT1A9, SLCO1B1, and ABCB1, can affect fluoroquinolones pharmacokinetic parameters such as area under the curve (AUC), creatinine clearance (CCr), maximum plasma concentration (Cmax), half-life (t1/2) and peak time (tmax) of fluoroquinolones.

DOI: 10.3389/fphar.2022.1063413
PMCID: PMC9798452
PMID: 36588725

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

50. **Safety, effectiveness, and adherence of a short and all-oral treatment regimen for the treatment of rifampicin-resistant tuberculosis in Niger: a study protocol of a pragmatic randomised clinical trial with stratified block randomisation.**

Trials. 2022 Dec 13;23(1):1011. doi: 10.1186/s13063-022-06912-7.

Souleymane MB(1), Decroo T(2)(3), Soumana A(4), Maman Lawan I(5), Gagara-Issoufou A(6), Halidou-Moussa S(7), Ortuño-Gutiérrez N(8), Adehossi E(6), Mamadou S(6), Van Deun A(9), Piubello A(5)(8).

BACKGROUND: Rifampicin-resistant tuberculosis (RR-TB) treatment requires combination treatment, which frequently causes serious adverse events and globally results in not much more than 60% treatment success. In Niger, a high cure rate was obtained with a RR-TB treatment strategy based on a second-line injectable drug (SLID)-containing Short Treatment Regimen (STR), with linezolid replacing the SLID in patients with ototoxicity. Given the availability of novel anti-tuberculosis drugs, WHO recommends all-oral RR-TB treatment. Considering the high level of success with the Niger treatment strategy, it would only be justified to replace it in case robust evidence shows that the WHO all-oral bedaquiline/linezolid (BDQ/LZD)-containing STR (experimental arm) performs

better than the Niger RR-TB treatment strategy, (control arm) in terms of safety, effectiveness and adherence.
METHODS: A pragmatic randomised clinical trial (RCT) using stratified block randomisation, conducted between April 2021 and March 2024, prospectively enrols participants diagnosed with RR-TB in one of the four RR-TB units of the nation. Depending of the month in which patients are diagnosed with RR-TB, patients with FQ-susceptible RR-TB are enrolled in either the experimental arm or control arm.
DISCUSSION: To increase the feasibility of conducting a RCT, embedded in routine activities of all Niger's RR-TB Units, we used a creative trial design. We randomised by monthly blocks, whereby the regimen used changes every month, using the month of RR-TB diagnosis as stratifying variable. This approach was deemed feasible for Niger's national tuberculosis programme, as it simplifies the work of the clinicians running the RR-TB units. Our creative design may serve as an example for other national programs. Findings will inform national and international RR-TB treatment guidelines, and will also strengthen the evidence-base on how to develop robust RR-TB treatment regimens.
TRIAL REGISTRATION: Pan African Clinical Trial Register PACTR202203645724919 . Registered on 15 March 2022.

DOI: 10.1186/s13063-022-06912-7
PMCID: PMC9746149
PMID: 36514153 [Indexed for MEDLINE]

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

51. **Pharmacodynamics and Bactericidal Activity of Combination Regimens in Pulmonary Tuberculosis: Application to Bedaquiline-Pretomanid-Pyrazinamide.**

Antimicrob Agents Chemother. 2022 Dec 20;66(12):e0089822. doi: 10.1128/aac.00898-22. Epub 2022 Nov 15.

Lyons MA(1).

A critical barrier to codevelopment of tuberculosis (TB) regimens is a limited ability to identify optimal drug and dose combinations in early-phase clinical testing. While pharmacokinetic-pharmacodynamic (PKPD) target attainment is the primary tool for exposure-response optimization of TB drugs, the PD target is a static index that does not distinguish individual drug contributions to the efficacy of a multidrug combination. A PKPD model of bedaquiline-pretomanid-pyrazinamide (BPaZ) for the treatment of pulmonary TB was

developed as part of a dynamic exposure-response approach to regimen development. The model describes a time course relationship between the drug concentrations in plasma and their individual as well as their combined effect on sputum bacillary load assessed by solid culture CFU counts and liquid culture time to positivity (TTP). The model parameters were estimated using data from the phase 2A studies NC-001-(J-M-Pa-Z) and NC-003-(C-J-Pa-Z). The results included a characterization of BPaZ activity as the most and least sensitive to changes in pyrazinamide and bedaquiline exposures, respectively, with antagonistic activity of BPa compensated by synergistic activity of BZ and PaZ. Simulations of the NC-003 study population with once-daily bedaquiline at 200 mg, pretomanid at 200 mg, and pyrazinamide at 1,500 mg showed BPaZ would require 3 months to attain liquid culture negativity in 90% of participants. These results for BPaZ were intended to be an example application with the general approach aimed at entirely novel drug combinations from a growing pipeline of new and repurposed TB drugs.

DOI: 10.1128/aac.00898-22
PMCID: PMC9765268
PMID: 36377952 [Indexed for MEDLINE]

Conflict of interest statement: The author declares no conflict of interest.

52. **Distribution and frequency of common mutations in rpoB gene of Mycobacterium tuberculosis detected by Xpert MTB/RIF and identification of residential areas of rifampicin resistant-TB cases: A first retrospective study from Mizoram, Northeast India.**

J Clin Tuberc Other Mycobact Dis. 2022 Nov 24;29:100342. doi: 10.1016/j.jctube.2022.100342. eCollection 2022 Dec.

Sailo CV(1)(2), Lalremruata R(2), Sanga Z(3), Fela V(3), Kharkongor F(3), Chhakchhuak Z(4), Chhakchhuak L(5), Nemi L(6), Zothanzama J(1), Kumar NS(1).

BACKGROUND: Rifampicin resistance (RR) is a surrogate marker of multidrug-resistant tuberculosis. The aim of this study is to determine the frequency of the commonly mutated probes for rpoB gene and locate the residential areas of the Rifampicin Resistant-TB (RR-TB) patients in a high endemic zone of Northeast India.
METHODS: Archived data of 13,454 Xpert MTB/RIF reports were evaluated retrospectively between 2014 and 2021. Socio-demographic and available clinical information were reviewed and analyzed for RR-TB cases only. Logistic Regression was used to analyze the parameters with respect to probe types. P-value ≤ 0.05 was considered to be statistically significant.

RESULTS: 2,894 patients had Mycobacterium tuberculosis infection out of which 460 were RR-TB, which was most prevalent among 25-34 years. The most common mutation occurred in probe A (25.9 %) followed by E (23.5 %), D (9.8 %), B (2.6 %) and the least in C (0.2 %). High prevalence (34.3 %) of probe mutation combinations were also found: probes AB (0.4 %), AD (32.8 %), AE (0.4 %), DE (0.2 %) and ADE (0.4 %). Seventeen patients (3.7 %) were found without any missing probes. RR-TB patients were mostly located in Aizawl North -III, South -II and East -II constituencies.
CONCLUSION: This study provides genetic pattern of drug resistance accountable for RR over the past years in Mizoram which will help local clinicians in the initiation of correct treatment. Also, our findings provide a baseline data on the magnitude of RR-TB within the state and identification of the residential areas can help local health authorities in planning surveillance programs to control the spread of RR-TB.

DOI: 10.1016/j.jctube.2022.100342
PMCID: PMC9707063
PMID: 36457842

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

53. **Evaluation of three alternatives cost-effective culture media for Mycobacterium tuberculosis detection and drug susceptibility determination using the microscopic observation drug susceptibility (MODS) assay.**

Tuberculosis (Edinb). 2022 Dec;137:102273. doi: 10.1016/j.tube.2022.102273. Epub 2022 Nov 14.

Rodriguez J(1), Alcántara R(2), Rodríguez J(1), Vargas J(3), Roncal E(1), Antiparra R(1), Gilman RH(4), Grandjean L(5), Moore D(6), Zimic M(1), Sheen P(7).

Tuberculosis phenotypic detection assays are commonly used in low-resource countries. Therefore, reliable detection methods are crucial for early diagnosis and treatment. The microscopic observation drug susceptibility (MODS) assay is a culture-based test to detect Mycobacterium tuberculosis and characterize drug resistance in 7-10 days directly from sputum. The use of MODS is limited by the availability of supplies necessary for preparing the enriched culture. In this study, we evaluated three dry culture media that are easier to produce and

cheaper than the standard one used in MODS [1]: an unsterilized powder-based mixed (Boldú et al., 2007) [2], a sterile-lyophilized medium, and (Sengstake et al., 2017) [3] an irradiated powder-based mixed. Mycobacterial growth and drug susceptibility were evaluated for rifampin, isoniazid, and pyrazinamide (PZA). The alternative cultures were evaluated using 282 sputum samples with positive acid-fast smears. No significant differences were observed in the positivity test rates. The positivity time showed high correlations (Rho) of 0.925, 0.889, and 0.866 between each of the three alternative media and the standard. Susceptibility testing for MDR and PZA showed an excellent concordance of 1 compared to the reference test. These results demonstrate that dry culture media are appropriate and advantageous for use in MODS in low-resource settings.

DOI: 10.1016/j.tube.2022.102273
PMID: 36403561 [Indexed for MEDLINE]

54. **Low Body Mass Index at Treatment Initiation and Rifampicin-Resistant Tuberculosis Treatment Outcomes: An Individual Participant Data Meta-Analysis.**

Clin Infect Dis. 2022 Dec 19;75(12):2201-2210. doi: 10.1093/cid/ciac322.

Campbell JR(1), Chan ED(2)(3)(4), Falzon D(5), Trajman A(6)(7), Keshavjee S(8), Leung CC(9), Miller AC(8), Monedero-Recuero I(10), Rodrigues DS(11), Seo H(12), Baghaei P(13), Udwadia Z(14), Viiklepp P(15), Bastos M(1), Menzies D(1).

BACKGROUND: The impact of low body mass index (BMI) at initiation of rifampicin-resistant tuberculosis (RR-TB) treatment on outcomes is uncertain. We evaluated the association between BMI at RR-TB treatment initiation and end-of-treatment outcomes.
METHODS: We performed an individual participant data meta-analysis of adults aged ≥18 years with RR-TB whose BMI was documented at treatment initiation. We compared odds of any unfavorable treatment outcome, mortality, or failure/recurrence between patients who were underweight (BMI <18.5 kg/m2) and not underweight. Adjusted odds ratios (aORs) and 95% confidence intervals (CIs) were estimated using logistic regression, with matching on demographic, clinical, and treatment-related factors. We evaluated effect modification by human immunodeficiency virus (HIV) status and other variables using likelihood ratio tests. We also estimated cumulative incidence of mortality during treatment stratified by HIV.
RESULTS: Overall, 5148 patients were included; 1702 (33%) were underweight at treatment initiation. The median (interquartile range) age was 37 years (29 to 47), and 455 (9%) had HIV. Compared with nonunderweight patients, the aOR among

underweight patients was 1.7 (95% CI, 1.4-1.9) for any unfavorable outcome, 3.1 (2.4-3.9) for death, and 1.6 (1.2-2.0) for failure/recurrence. Significant effect modification was found for World Health Organization region of treatment. Among HIV-negative patients, 24-month mortality was 14.8% (95% CI, 12.7%-17.3%) for underweight and 5.6% (4.5%-7.0%) for not underweight patients. Among patients with HIV, corresponding values were 33.0% (25.6%-42.6%) and 20.9% (14.1%-27.6%).
CONCLUSIONS: Low BMI at treatment initiation for RR-TB is associated with increased odds of unfavorable treatment outcome, particularly mortality.

DOI: 10.1093/cid/ciac322
PMID: 35476134 [Indexed for MEDLINE]

Conflict of interest statement: Potential conflicts of interest. D. F. is a staff member of the World Health Organization (WHO). I. M. R. reports consulting fees from WHO, DR-TB, for the regional Green Light Committee (rGLC) mission in Pakistan, Yemen, Syria, Jordan, and Lebanon; WHO, drug-resistant tuberculosis(DR-TB) guideline writing for Eastern Mediterranean Regional Office; and WHO, situational analysis of the 10 DR-TB high burden countries after the United Nations High Level Meeting, all paid to self; payment or honoraria for international DR-TB trainings at The Union (on line), International tuberculosis (TB) infection training at The Union (on line), and DR-TB training for Middle East Response countries at international organization for migration, all paid to self; payment for expert testimony from Teladoc Health International (clinical cases, second medical opinion in complex infectious diseases management), paid to self; and participation on Novel triple-dose tuberculosis retreatment regimens (TriDoRe; NCT04260477) and received no payment. S. K. reports support for the present study from the Eli Lilly Foundation (grant to Brigham & Women's Hospital to support multidrug-resistant tuberculosis (MDR-TB) program supports in Russia; The donor had no involvement in data collection, manuscript preparation, or interpretation.) and Advance Access & Delivery (nongovernmental organization) as a board member. D. M. reports support for the present manuscript through funding provided in 2018–2019 by WHO, ATS/ERS/CDC/IDSA, for establishment of the individual participant data dataset, no funding for this analysis, paid to their institution; participation in scientific advisory committee for 2 trials of MDRTB in South Africa (no honoraria); and served as chair of the Canadian Thoracic Society–TB Committee (unpaid). A. T. reports a grant from Brazilian Ministry of Science, Technology and Innovation, as a direct grant to self outside of the submitted work. 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.

55. **Tailored TB preventive treatment for drug-resistant TB - failing the test for appropriateness?**

Int J Tuberc Lung Dis. 2022 Dec 1;26(12):1198. doi: 10.5588/ijtld.22.0522.

Noeske J(1), Kuaban C(2).

Comment on
Int J Tuberc Lung Dis. 2022 Sep 1;26(9):900-901.

DOI: 10.5588/ijtld.22.0522
PMID: 36447329 [Indexed for MEDLINE]

56. **The Struggle to End a Millennia-Long Pandemic: Novel Candidate and Repurposed Drugs for the Treatment of Tuberculosis.**

Drugs. 2022 Dec;82(18):1695-1715. doi: 10.1007/s40265-022-01817-w. Epub 2022 Dec 7.

Edwards BD(1), Field SK(2).

This article provides an encompassing review of the current pipeline of putative and developed treatments for tuberculosis, including multidrug-resistant strains. The review has organized each compound according to its site of activity. To provide context, mention of drugs within current recommended treatment regimens is made, thereafter followed by discussion on recently developed and upcoming molecules at established and novel targets. The review is designed to provide a clinically applicable understanding of the compounds that are deemed most currently relevant, including those already under clinical study and those that have shown promising pre-clinical results. An extensive review of the efficacy and safety data for key contemporary drugs already incorporated into treatment regimens, such as bedaquiline, pretomanid, and linezolid, is provided. The three levels of the bacterial cell wall (mycolic acid, arabinogalactan, and peptidoglycan layers) are highlighted and important compounds designed to target each layer are delineated. Amongst others, the highly optimistic and potent anti-mycobacterial activity of agents such as BTZ-043, PBTZ 169, and OPC-167832 are emphasized. The evolving spectrum of oxazolidinones, such as sutezolid, delpazolid, and TBI-223, all aiming to exceed the efficacy achieved with linezolid yet offer a safer alternative to the

potential toxicity, are reviewed. New and exciting prospective agents with novel mechanisms of impact against TB, including 3-aminomethyl benzoxaboroles and telacebec, are underscored. We describe new diaryloquinolines in development, striving to build on the immense success of bedaquiline. Finally, we discuss some of these compounds that have shown encouraging additive or synergistic benefit when used in combination, providing some promise for the future in treating this ancient scourge.

DOI: 10.1007/s40265-022-01817-w
PMCID: PMC9734533
PMID: 36479687 [Indexed for MEDLINE]

Conflict of interest statement: Neither Brett Edwards nor Stephen Field has any conflicts of interest related to the contents of this article.

57. **Elucidating the function of hypothetical PE_PGRS45 protein of Mycobacterium tuberculosis as an oxido-reductase: a potential target for drug repurposing for the treatment of tuberculosis.**

J Biomol Struct Dyn. 2022 Nov 30:1-17. doi: 10.1080/07391102.2022.2151514. Online ahead of print.

Joshi H(1), Sharma S(2), Sharma M(2).

Mycobacterium tuberculosis (Mtb) encodes a total of 67 PE_PGRS proteins and definite functions of many of them are still unknown. This study reports PE_PGRS45 (Rv2615c) protein from Mtb as NADPH dependent oxido-reductase having substrate specificity for fatty acyl Coenzyme A. Computational studies predicted PE_PGRS45 to be an integral membrane protein of Mtb. Expression of PE_PGRS45 in non-pathogenic Mycobacterium smegmatis, which does not possess PE_PGRS genes, confirmed its membrane localization. This protein was observed to have NADPH binding motif. Experimental validation confirmed its NADPH dependent oxido-reductase activity (Km value = 34.85 ± 9.478 µM, Vmax = 96.77 ± 7.184 nmol/min/mg of protein). Therefore, its potential to be targeted by first line anti-tubercular drug Isoniazid (INH) was investigated. INH was predicted to bind within the active site of PE_PGRS45 protein and experiments validated its inhibitory effect on the oxido-reductase activity of PE_PGRS45 with IC50/Ki values of 5.66 µM. Mtb is resistant to first line drugs including INH. Therefore, to address the problem of drug resistant TB, docking and Molecular Dynamics (MD) simulation studies between PE_PGRS45 and three drugs

(Entacapone, Tolcapone and Verapamil) which are being used in Parkinson's and hypertension treatment were performed. PE_PGRS45 bound the three drugs with similar or better affinity in comparison to INH. Additionally, INH and these drugs bound within the same active site of PE_PGRS45. This study discovered Mtb's PE_PGRS45 protein to have an oxido-reductase activity and could be targeted by drugs that can be repurposed for TB treatment. Furthermore, in-vitro and in-vivo validation will aid in drug-resistant TB treatment.
HIGHLIGHTSIn-silico and in-vitro studies of hypothetical protein PE_PGRS45 (Rv2615c) of Mycobacterium tuberculosis (Mtb) reveals it to be an integral membrane proteinPE_PGRS45 protein has substrate specificity for fatty acyl Coenzyme A (fatty acyl CoA) and possess NADPH dependent oxido-reductase activityDocking and simulation studies revealed that first line anti-tubercular drug Isoniazid (INH) and other drugs with anti-TB property have strong affinity for PE_PGRS45 proteinOxido-reductase activity of PE_PGRS45 protein is inhibited by INHPE_PGRS45 protein could be targeted by drugs that can be repurposed for TB treatmentCommunicated by Ramaswamy H. Sarma.

DOI: 10.1080/07391102.2022.2151514
PMID: 36448553

58. **Prevention and management of hearing loss in patients receiving ototoxic medications.**

Bull World Health Organ. 2022 Dec 1;100(12):789-796A. doi: 10.2471/BLT.21.286823. Epub 2022 Sep 2.

Lindeborg MM(1), Jung DH(2), Chan DK(1), Mitnick CD(3).

Following the efforts of patient advocates, the World Health Organization published updated guidelines for management of multidrug-resistant tuberculosis in 2018 that advised against the routine use of ototoxic second-line injectable drugs (amikacin, capreomycin and kanamycin). Although hearing loss is no longer considered an unavoidable harm for patients with multidrug-resistant tuberculosis, ototoxic medications continue to be used for several infectious and oncological disorders around the world. These drugs contribute to more than a half a million cases of hearing loss worldwide annually. Currently, there are no international standards for preventing and managing hearing loss associated with ototoxic medications. We present recent data on the prevention and management of hearing loss related to these drugs and highlight the variability in care across settings. More importantly, we aim to provide an evidence-based framework for evaluating, screening and preventing ototoxicity. Finally, we identify avenues for future research so that patients no longer have to choose between hearing loss and a disease cure. There remain significant gaps in our

understanding about optimal screening and treatment of ototoxic hearing loss. Here we aim to inspire future international guidelines to address gaps in ototoxicity care and establish research agendas for eliminating ototoxic medications.

DOI: 10.2471/BLT.21.286823
PMCID: PMC9706352
PMID: 36466201 [Indexed for MEDLINE]

59. **Host cell transcriptomic response to the multidrug-resistant Mycobacterium tuberculosis clonal outbreak Beijing strain reveals its pathogenic features.**

Virulence. 2022 Dec;13(1):1810-1826. doi: 10.1080/21505594.2022.2135268.

Prombutara P(1)(2)(3), Adriansyah Putra Siregar T(3)(4), Laopanupong T(3), Kanjanasirirat P(5), Khumpanied T(5), Borwornpinyo S(5)(6), Rai A(7), Chaiprasert A(8)(9), Palittapongarnpim P(3)(10)(11), Ponpuak M(3)(10).

The upsurge of multidrug-resistant infections has rendered tuberculosis the principal cause of death among infectious diseases. A clonal outbreak multidrug-resistant triggering strain of Mycobacterium tuberculosis was identified in Kanchanaburi Province, labelled "MKR superspreader," which was found to subsequently spread to other regions, as revealed by prior epidemiological reports in Thailand. Herein, we showed that the MKR displayed a higher growth rate upon infection into host macrophages in comparison with the H37Rv reference strain. To further elucidate MKR's biology, we utilized RNA-Seq and differential gene expression analyses to identify host factors involved in the intracellular viability of the MKR. A set of host genes function in the cellular response to lipid pathway was found to be uniquely up-regulated in host macrophages infected with the MKR, but not those infected with H37Rv. Within this set of genes, the IL-36 cytokines which regulate host cell cholesterol metabolism and resistance against mycobacteria attracted our interest, as our previous study revealed that the MKR elevated genes associated with cholesterol breakdown during its growth inside host macrophages. Indeed, when comparing macrophages infected with the MKR to H37Rv-infected cells, our RNA-Seq data showed that the expression ratio of IL-36RN, the negative regulator of the IL-36 pathway, to that of IL-36G was greater in macrophages infected with the MKR. Furthermore, the MKR's intracellular survival and increased intracellular cholesterol level in the MKR-infected macrophages were diminished with decreased IL-36RN expression. Overall, our results indicated that IL-36RN could serve as a new target against this emerging multidrug-resistant M. tuberculosis strain.

DOI: 10.1080/21505594.2022.2135268
PMCID: PMC9578452
PMID: 36242542 [Indexed for MEDLINE]

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

60. **Predictors of unfavourable treatment outcome in patients diagnosed with drug-resistant tuberculosis in the Torres Strait / Papua New Guinea border region.**

PLoS One. 2022 Dec 9;17(12):e0266436. doi: 10.1371/journal.pone.0266436. eCollection 2022.

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

Drug-resistant tuberculosis (DR-TB) is an ongoing challenge in the Torres Strait Islands (TSI) / Papua New Guinea (PNG) border region. Treatment success rates have historically been poor for patients diagnosed with DR-TB, leading to increased transmission. This study aimed to identify variables associated with unfavourable outcome in patients diagnosed with DR-TB to inform programmatic improvements. A retrospective study of all DR-TB cases who presented to Australian health facilities in the Torres Strait between 1 March 2000 and 31 March 2020 was performed. This time period covers four distinct TB programmatic approaches which reflect Australian and Queensland Government decisions on TB management in this remote region. Univariate and multivariate predictors of unfavourable outcome were analysed. Unfavourable outcome was defined as lost to follow up, treatment failure and death. Successful outcome was defined as cure and treatment completion. In total, 133 patients with resistance to at least one TB drug were identified. The vast majority (123/133; 92%) of DR-TB patients had pulmonary involvement; and of these, 41% (50/123) had both pulmonary and extrapulmonary TB. Unfavourable outcomes were observed in 29% (39/133) of patients. Patients living with human immunodeficiency virus, renal disease or diabetes (4/133; 4/133; 3/133) had an increased frequency of unfavourable outcome ($p < 0.05$), but the numbers were small. Among all 133 DR-TB patients, 41% had a low lymphocyte count, which was significantly associated with unfavourable outcome ($p < 0.05$). We noted a 50% increase in successful outcomes achieved in the 2016-2020 programmatic period, compared to earlier periods (OR 5.3, 95% Confidence Interval [1.3, 20.4]). Being a close contact of a known TB case was associated with improved outcome. While DR-TB treatment outcomes have improved over time, enhanced surveillance for DR-TB, better cross border collaboration

and consistent diagnosis and management of comorbidities and other risk factors should further improve patient care and outcomes.

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PMCID: PMC9733860
PMID: 36490236 [Indexed for MEDLINE]

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

61. **Tuberculosis treatment failure associated with evolution of antibiotic resilience.**

Science. 2022 Dec 9;378(6624):1111-1118. doi: 10.1126/science.abq2787. Epub 2022 Dec 8.

Liu Q(#)(1), Zhu J(#)(1), Dulberger CL(1)(2)(3), Stanley S(1), Wilson S(2), Chung ES(4)(5), Wang X(1), Culviner P(1), Liu YJ(1), Hicks ND(1), Babunovic GH(1), Giffen SR(1), Aldridge BB(4)(5), Garner EC(2), Rubin EJ(1), Chao MC(1), Fortune SM(1)(6).

The widespread use of antibiotics has placed bacterial pathogens under intense pressure to evolve new survival mechanisms. Genomic analysis of 51,229 Mycobacterium tuberculosis (Mtb)clinical isolates has identified an essential transcriptional regulator, Rv1830, herein called resR for resilience regulator, as a frequent target of positive (adaptive) selection. resR mutants do not show canonical drug resistance or drug tolerance but instead shorten the post-antibiotic effect, meaning that they enable Mtb to resume growth after drug exposure substantially faster than wild-type strains. We refer to this phenotype as antibiotic resilience. ResR acts in a regulatory cascade with other transcription factors controlling cell growth and division, which are also under positive selection in clinical isolates of Mtb. Mutations of these genes are associated with treatment failure and the acquisition of canonical drug resistance.

DOI: 10.1126/science.abq2787
PMID: 36480634 [Indexed for MEDLINE]

62. **Impacts of Medical Security Level on Treatment Outcomes of Drug-Resistant Tuberculosis: Evidence from Wuhan City, China.**

Patient Prefer Adherence. 2022 Dec 20;16:3341-3355. doi: 10.2147/PPA.S389231. eCollection 2022.

Liu X(#)(1), Lin KH(#)(1), Li YH(2), Jiang JN(3), Zhong ZD(1), Xiong YB(1), Zhou J(1), Xiang L(1)(4).

BACKGROUND: Drug-resistant tuberculosis (DR-TB) is an increasingly serious global issue. DR-TB has a lower success rate and more severe interruption of treatment than ordinary tuberculosis. Incomplete treatment not only reduces recovery rate in DR-TB patients but also increases the spread of DR-TB. Optimizing medical security policies for DR-TB can reduce the economic burden of patients and can thereby improve treatment success rate.
METHODS: Patients with DR-TB who were registered in Wuhan Center for Tuberculosis Control and Prevention from January 2016 to December 2019 were selected as research subjects. General descriptive statistical analysis methods were used in analyzing patients' treatment outcomes and medical security compensation rate. The binary logistic regression was used in analyzing the impacts of medical security level on treatment outcomes of DR-TB.
RESULTS: A total of 409 DR-TB patients were included in the study, and the refusal rate was 12.47%. The treatment success rate was only 37.09% for patients who started treatment and had treatment outcomes. The total out-of-pocket expenses (OOPs) per capita for DR-TB patients were 13,005.61 Chinese yuan. The outpatient effective compensation ratio (ECR) of DR-TB patients was only 51.04%. The outpatient ECR of DR-TB with subsidies of public health projects (SPHPs) were nearly 80% higher than those without SPHP. high outpatient ECR helped optimize treatment outcomes ($P < 0.001$, OR = 1.038). The inpatient ECR had no effect on patients' treatment outcomes ($P = 0.158$, OR = 0.986).
CONCLUSION: Many DR-TB patients did not receive complete treatment. The key breakthrough point in improving DR-TB treatment outcomes is to optimize the outpatient medical insurance compensation policy. Including the costs of DR-TB in expenses for severe diseases in outpatient care is recommended, and financial investment should be appropriately increased to ensure the high coverage ratio of subsidies for public health projects.

DOI: 10.2147/PPA.S389231
PMCID: PMC9789709
PMID: 36573226

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

63. **The ddn Trp20Stop Mutation and Its Association with Lineage 4.5 and Resistance to Delamanid and Pretomanid in Mycobacterium tuberculosis.**

Antimicrob Agents Chemother. 2022 Dec 20;66(12):e0102622. doi: 10.1128/aac.01026-22. Epub 2022 Nov 21.

Mansjö M(1), Karlsson Lindsjö O(1), Grönfors Seeth C(1), Groenheit R(1), Werngren J(1).

High-confidence resistance mutations for new and repurposed anti-TB drugs, such as delamanid (DLM) and pretomanid (Pa), are rare and more data are needed in order to correctly interpret the results generated by genotypic drug susceptibility testing. In this study performed on clinical Mycobacterium tuberculosis complex isolates, we report that in the Swedish strain collection the ddn mutation Trp20Stop is found exclusively among DLM and Pa resistant (Pa MIC >16 mg/L) isolates assigned to lineage 4.5.

DOI: 10.1128/aac.01026-22
PMCID: PMC9765023
PMID: 36409105 [Indexed for MEDLINE]

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

64. **Attitudes of Healthcare Workers about Prevention and Control of Nosocomial Multidrug-Resistant Tuberculosis Infection in Two Top-Ranked Tuberculosis Specialized Public Hospitals of Ethiopia.**

Can J Infect Dis Med Microbiol. 2022 Dec 14;2022:5266347. doi: 10.1155/2022/5266347. eCollection 2022.

Kebede T(1)(2), Molla Sisay M(3).

BACKGROUND: Tuberculosis (TB) exists as a human curse since antiquity. Around 9.5 million cases and 1.5 million deaths were reported due to TB in 2021. Ethiopia is one of the high-burdenmultidrug-resistant (MDR) TB countries. MDR-TB is acquired either by poor adherence to treatment or by primary infection with a drug-resistant strain, which has a high transmission rate from patients to healthcare workers (HCWs). Hospital outbreaks of MDR-TB are common in Africa. Hence, this study aimed to score the attitude of HCWs working in the two

nationally top-rankedTB-specialized hospitals in Ethiopia, Saint Peter's and ALERT TB-specialized public hospitals about the infection prevention and control (IPC) of nosocomial MDR-TB.
METHODS: A cross-sectional study was conducted from December 1, 2020, to March 31, 2021. A simple random sampling method was applied to select 384 HCWs. The data collection tool was a self-administered interview structured questionnaire. The data were analyzed using SPSS software. Descriptive statistics were applied to score attitude. Bivariate and multivariable logistic regression models were performed to identify the independent determinants of attitude. The odds ratio was used to test the degree of association between variables at a 95% confidence interval (CI). The level of statistical significance was fixed at p value < 0.05.
RESULTS: Among the respondents, 87% of the HCWs held favourable attitudes about the nosocomial MDR-TB-IPC. The favourable attitude score had a significant association with the monthly salary earned between 7001 and 9000 ETB (Ethiopian Birr) (AOR = 3.34, 95% CI: 1.11, 10.05) and the previous training obtained on TB/MDR-TB (AOR = 2.96, 95% CI: 1.32, 6.62).
CONCLUSIONS: Almost one in seven HCWs has an unfavourable attitude. Prior training received and earning monthly income above 7000 ETB are independent determinants of a favourable attitude score. Refreshment training and a reasonable increment in monthly income should be strengthened in TB-specialized hospitals in Ethiopia.

DOI: 10.1155/2022/5266347
PMCID: PMC9771643
PMID: 36570677

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

65. **Mycobacterium Fluoroquinolone Resistance Protein D (MfpD), a GTPase-Activating Protein of GTPase MfpB, Is Involved in Fluoroquinolones Potency.**

Microbiol Spectr. 2022 Dec 21;10(6):e0209822. doi: 10.1128/spectrum.02098-22. Epub 2022 Dec 1.

Huang Y(1), Yan S(1), Li Y(1), Ai X(1), Yu X(1), Ge Y(1), Lv X(1), Fan L(2), Xie J(1).

Tuberculosis (TB) caused by Mycobacterium tuberculosis infection remains one of the most serious global health problems. Fluoroquinolones (FQs) are an important

component of drug regimens against multidrug-resistant tuberculosis, but challenged by the emergence of FQ-resistant strains. Mycobacterium fluoroquinolone resistance protein A (MfpA) is a pentapeptide protein that confers resistance to FQs. MfpA is the fifth gene in the mfp operon among most Mycobacterium, implying other mfp genes might regulate the activity of MfpA. To elucidate the function of this operon, we constructed deletion mutants and rescued strains and found that MfpD is a GTPase-activating protein (GAP) involved in FQs activity. We showed that the recombinant strains overexpressing mfpD became more sensitive to FQs, whereas an mfpD deletion mutant was more resistant to FQs. By using site-directed mutagenesis and mycobacterial protein fragment complementation, we genetically demonstrated that mfpD participated in FQs susceptibility via directly acting on mfpB. We further biochemically demonstrated that MfpD was a GAP capable of stimulating the GTPase activity of MfpB. Our studies suggest that MfpD, a GAP of MfpB, is involved in MfpA-mediated FQs resistance. The function of MfpD adds new insights into the role of the mfp operon in Mycobacterium fluoroquinolone resistance. IMPORTANCE Tuberculosis is one of the leading causes of morbidity and mortality worldwide largely due to increasingly prevalent drug-resistant strains. Fluoroquinolones are important antibiotics used for treating multidrug-resistant tuberculosis (MDR-TB). The resistance mechanism mediated by the Mycobacterium fluoroquinolone resistance protein (MfpA) is unique in Mycobacterium. However, the regulatory mechanism of MfpA remains largely unclear. In this study, we first report that MfpD acts as a GAP for MfpB and characterize a novel pathway that controls Mycobacterium small G proteins. Our findings provide new insights into the regulation of MfpA and inspiration for new candidate targets for the discovery and development of anti-TB drugs.

DOI: 10.1128/spectrum.02098-22
PMCID: PMC9769811
PMID: 36453945 [Indexed for MEDLINE]

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

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

Microbiol Spectr. 2022 Dec 21;10(6):e0259222. doi: 10.1128/spectrum.02592-22. Epub 2022 Oct 31.

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

The complexity and duration of tuberculosis (TB) treatment contributes to the

emergence of drug resistant tuberculosis (DR-TB) and drug-associated side effects. Alternate chemotherapeutic agents are needed to shorten the time and improve efficacy of current treatment. In this study, we have assessed the antitubercular activity of NSC19723, a benzaldehyde thiosemicarbazone molecule. NSC19723 is structurally similar to thiacetazone (TAC), a second-line anti-TB drug used to treat individuals with DR-TB. NSC19723 displayed better MIC values than TAC against Mycobacterium tuberculosis and Mycobacterium bovis BCG. In our checkerboard experiments, NSC19723 displayed better profiles than TAC in combination with known first-line and recently approved drugs. Mechanistic studies revealed that NSC19723 inhibits mycolic acid biosynthesis by targeting the HadABC complex. Computational studies revealed that the binding pocket of HadAB is similarly occupied by NSC19723 and TAC. NSC19723 also improved the efficacy of isoniazid in macrophages and mouse models of infection. Cumulatively, we have identified a benzaldehyde thiosemicarbazone scaffold that improved the activity of TB drugs in liquid cultures, macrophages, and mice. IMPORTANCE Mycobacterium tuberculosis, the causative agent of TB is among the leading causes of death among infectious diseases in humans. This situation has worsened due to the failure of BCG vaccines and the increased number of cases with HIV-TB coinfections and drug-resistant strains. Another challenge in the field is the lengthy duration of therapy for drug-sensitive and -resistant TB. Here, we have deciphered the mechanism of action of NSC19723, benzaldehyde thiosemicarbazone. We show that NSC19723 targets HadABC complex and inhibits mycolic acid biosynthesis. We also show that NSC19723 enhances the activity of known drugs in liquid cultures, macrophages, and mice. We have also performed molecular docking studies to identify the interacting residues of HadAB with NSC19723. Taken together, we demonstrate that NSC19723, a benzaldehyde thiosemicarbazone, has better antitubercular activity than thiacetazone.

DOI: 10.1128/spectrum.02592-22
PMCID: PMC9769743
PMID: 36314972 [Indexed for MEDLINE]

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

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

Am J Audiol. 2022 Dec 9:1-11. doi: 10.1044/2022_AJA-22-00039. Online ahead of print.

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

PURPOSE: The aim of this study was to describe extended high-frequency (EHF)

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

DOI: 10.1044/2022_AJA-22-00039
PMID: 36490390

68. **Localization of Mycobacterium tuberculosis topoisomerase I C-terminal sequence motif required for inhibition by endogenous toxin MazF4.**

Front Microbiol. 2022 Dec 5;13:1032320. doi: 10.3389/fmicb.2022.1032320. eCollection 2022.

Garcia PK(1), Martinez Borrero R(1), Annamalai T(1)(2), Diaz E(1), Balarezo S(1), Tiwari PB(3), Tse-Dinh YC(1)(2).

Only about half the multi-drug resistant tuberculosis (MDR-TB) cases are successfully cured. Thus, there is an urgent need of new TB treatment against a novel target. Mycobacterium tuberculosis (Mtb) topoisomerase I (TopA) is the only type IA topoisomerase in this organism and has been validated as an essential target for TB drug discovery. Toxin-antitoxin (TA) systems participate as gene regulators within bacteria. The TA systems contribute to the long-term

dormancy of Mtb within the host-cell environment. Mtb's toxin MazF4 (Rv1495) that is part of the MazEF4 TA system has been shown to have dual activities as endoribonuclease and topoisomerase I inhibitor. We have developed a complementary assay using an Escherichia coli strain with temperature-sensitive topA mutation to provide new insights into the MazF4 action. The assay showed that E. coli is not sensitive to the endoribonuclease activity of Mtb MazF4 but became vulnerable to MazF4 growth inhibition when recombinant Mtb TopA relaxation activity is required for growth. Results from the complementation by Mtb TopA mutants with C-terminal deletions showed that the lysine-rich C-terminal tail is required for interaction with MazF4. Site-directed mutagenesis is utilized to identify two lysine residues within a conserved motif in this C-terminal tail that are critical for MazF4 inhibition. We performed molecular dynamics simulations to predict the Mtb TopA-MazF4 complex. Our simulation results show that the complex is stabilized by hydrogen bonds and electrostatic interactions established by residues in the TopA C-terminal tail including the two conserved lysines. The mechanism of Mtb TopA inhibition by MazF4 could be useful for the discovery of novel inhibitors against a new antibacterial target in pathogenic mycobacteria for treatment of both TB and diseases caused by the non-tuberculosis mycobacteria (NTM).

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PMCID: PMC9760754
PMID: 36545199

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

69. **High proportion of tuberculosis transmission among social contacts in rural China: a 12-year prospective population-based genomic epidemiological study.**

Emerg Microbes Infect. 2022 Dec;11(1):2102-2111. doi: 10.1080/22221751.2022.2112912.

Li M(1)(2), Guo M(3), Peng Y(4), Jiang Q(1)(5), Xia L(6), Zhong S(7), Qiu Y(3), Su X(7), Zhang S(6), Yang C(1)(8), Mijiti P(1), Mao Q(1), Takiff H(9), Li F(4), Chen C(6), Gao Q(1)(2).

ABSTRACTTuberculosis (TB) is more prevalent in rural than urban areas in China, and delineating TB transmission patterns in rural populations could improve TB

control. We conducted a prospective population-based study of culture-positive pulmonary TB patients diagnosed between July 1, 2009 and December 31, 2020 in two rural counties in China. Genomic clusters were defined with a threshold distance of 12-single-nucleotide-polymorphisms, based on whole-genome sequencing. Risk factors for clustering were identified by logistic regression. Transmission links were sought through epidemiological investigation of genomic-clustered patients. Of 1517 and 751 culture-positive pulmonary TB patients in Wusheng and Wuchang counties, respectively, 1289 and 699 strains were sequenced. Overall, 624 (31.4%, 624/1988) patients were grouped into 225 genomic clusters. Epidemiological links were confirmed in 41.8% (196/469) of clustered isolates, including family (32.7%, 64/196) and social contacts (67.3%, 132/196). Social contacts were generally with relatives, within the community or in shared aggregated settings outside the community, but the proportion of clustered contacts in each category differed between the two sites. The time interval between diagnosis of student cases and contacts was significantly shorter than family and social contacts, probably due to enhanced student contact screening. Transmission of multidrug-resistant (MDR) strains was likely responsible for 81.4% (83/102) of MDR-TB cases, with minimal acquisition of additional resistance mutations. A large proportion of TB transmission in rural China occurred among social contacts, suggesting that active screening and aggressive contact tracing could benefit TB control, but contact screening should be tailored to local patterns of social interactions.

DOI: 10.1080/22221751.2022.2112912
PMCID: PMC9448380
PMID: 35950916 [Indexed for MEDLINE]

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

70. **Machine learning and radiomics for the prediction of multidrug resistance in cavitary pulmonary tuberculosis: a multicentre study.**

Eur Radiol. 2023 Jan;33(1):391-400. doi: 10.1007/s00330-022-08997-9. Epub 2022 Jul 19.

Li Y(1), Wang B(2), Wen L(3), Li H(3), He F(4), Wu J(1), Gao S(2), Hou D(5).

OBJECTIVES: Multidrug-resistant tuberculosis (MDR-TB) is a major challenge to global health security. Early identification of MDR-TB patients increases the likelihood of treatment success and interrupts transmission. We aimed to develop a predictive model for MDR to cavitary pulmonary TB using CT radiomics features. METHODS: This retrospective study included 257 consecutive patients with proven

active cavitary TB (training cohort: 187 patients from Beijing Chest Hospital; testing cohort: 70 patients from Infectious Disease Hospital of Heilongjiang Province). Radiomics features were extracted from the segmented cavitation. A radiomics model was constructed to predict MDR using a random forest classifier. Meaningful clinical characteristics and subjective CT findings comprised the clinical model. The radiomics and clinical models were combined to create a combined model. ROC curves were used to validate the capability of the models in the training and testing cohorts.
RESULTS: Twenty-one radiomics features were selected as optimal predictors to build the model for predicting MDR-TB. The AUCs of the radiomics model were significantly higher than those of the clinical model in either the training cohort (0.844 versus 0.589, $p < 0.05$) or the testing cohort (0.829 versus 0.500, $p < 0.05$). The AUCs of the radiomics model were slightly lower than those of the combined model in the training cohort (0.844 versus 0.881, $p > 0.05$) and testing cohort (0.829 versus 0.834, $p > 0.05$), but there was no significant difference.
CONCLUSIONS: The radiomics model has the potential to predict MDR in cavitary TB patients and thus has the potential to be a diagnostic tool.
KEY POINTS: • This is the first study to build and validate models that distinguish MDR-TB from DS-TB with clinical and radiomics features based on cavitation. • The radiomics model demonstrated good performance and might potentially aid in prior TB characterisation treatment. • This noninvasive and convenient technique can be used as a diagnosis tool into routine clinical practice.

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PMCID: PMC9294743
PMID: 35852573 [Indexed for MEDLINE]

Conflict of interest statement: The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

71. **Mass spectrometry-based identification of new serum biomarkers in patients with latent infection pulmonary tuberculosis.**

Medicine (Baltimore). 2022 Dec 2;101(48):e32153. doi: 10.1097/MD.0000000000032153.

Li YX(1), Zheng KD(2), Duan Y(1), Liu HJ(1), Tang YQ(1), Wu J(3), Lin DZ(4), Zhang Z(2)(5).

Noninvasive and simple indicators for diagnosing latent tuberculosis (TB) infection (LTBI) and tracking progression from latent infection to active TB infection are still desperately needed. The aim of this study was to screen and identify possible biomarkers for diagnosing LTBI and monitoring the progression from latent infection to active TB infection, as well as to investigate the underlying processes and functions. To assess changes in metabolite composition associated with active tuberculosis infection in humans, whole blood supernatants were collected from patients with LTBI, drug-susceptible TB patients, drug-resistant TB patients, and healthy controls. The metabolites in all serum samples were extracted by oscillatory, deproteinization, and then detected by liquid chromatography-tandem mass spectrometry/MS analysis. Normalization by Pareto-scaling method, the difference analysis was carried out by Metaboanalyst 4.0 software, and 1-way analysis of variance analysis among groups showed that P-value < 0.05 was regarded as a different metabolite. To clarify the dynamic changes and functions of differential metabolites with disease progression, and explore its significance and mechanism as a marker by further cluster analysis, functional enrichment analysis, and relative content change analysis of differential metabolites. 65 metabolites were substantially different in four groups. Differential metabolites such as Inosine and Prostaglandin E1 may be important blood indicators for diagnosing mycobacterium tuberculosis latent infection, which were all tightly connected to amino acid metabolism, Biosynthesis of various secondary metabolites, Nucleotide metabolism, Endocrine system, Immune system, Lipid metabolism, and Nervous system. This study screened and identified Inosine, 16, 16-dimethyl-6-keto Prostaglandin E1, Theophylline, and Cotinine as potential serum biomarkers for diagnosing latent TB infection, and Cotinine as potential biomarkers for monitoring disease progression from healthy population to LTBI and then to active TB including drug-resistant TB infection and sensitive TB infection. Furthermore, this research provides a preliminary experimental basis to further investigate the development of metabolomics-based diagnosis of LTBI and monitoring the progress from latent infection to active TB infection.

DOI: 10.1097/MD.0000000000032153
PMCID: PMC9726300
PMID: 36482536 [Indexed for MEDLINE]

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

72. **Assessing Pretomanid for Tuberculosis (APT), a Randomized Phase 2 Trial of Pretomanid-containing Regimens for Drug-sensitive TB: 12-Week Results.**

Am J Respir Crit Care Med. 2022 Dec 1. doi: 10.1164/rccm.202208-1475OC. Online ahead of print.

Dooley KE(1), Hendricks B(2), Gupte N(3), Barnes G(4), Narunsky K(5), Whitelaw C(2), Smit T(2), Ignatius EH(6), Friedman A(2), Dorman SE(7), Dawson R(2); Assessing Pretomanid for Tuberculosis (APT) Study Team.

RATIONALE: Pretomanid is a new nitroimidazole with proven treatment-shortening efficacy in drug-resistant tuberculosis. Pretomanid-rifamycin-pyrazinamide combinations are potent in mice but have not been tested clinically. Rifampicin, but not rifabutin, reduces pretomanid exposures.
OBJECTIVE: Evaluate the safety and efficacy of pretomanid-rifamycin-pyrazinamide containing regimens among participants with drug-sensitive pulmonary tuberculosis.
METHODS: Phase 2 twelve-week open-label randomized trial of isoniazid, pyrazinamide, plus (a) pretomanid and rifampicin (Arm 1); (b) pretomanid and rifabutin (Arm 2) or (c) rifampicin and ethambutol (standard of care, Arm 3). Safety labs and sputum cultures were collected at Weeks 1, 2, 3, 4, 6, 8, 10, 12. Time to culture conversion on liquid media was the primary outcome.
RESULTS: Among 157 participants, 125 (80%) had cavitary disease. Median time to liquid culture negativity in the modified intention to treat (mITT) population (n=150) was 41 (Arm 1), 28 (Arm 2), and 55 (Arm 3) days (p=0.01)(adjusted hazard ratios of 1.41 (0.93-2.12, p=0.10), Arm 1 vs. Arm 3) and 1.89 (1.24-2.87, p=0.003, Arm 2 vs. Arm 3)). Eight-week liquid culture conversion was 79%, 89%, and 69%, respectively. Grade >3 adverse events occurred in 3/56 (5%), 5/53 (9%), and 2/56 (4%) of participants. Six participants were withdrawn owing to elevated transaminases (5 in Arm 2, 1 in Arm 1).There were 3 serious adverse events (Arm 2) and no deaths.
CONCLUSIONS: Pretomanid enhanced the microbiologic activity of rifamycin-pyrazinamide containing regimens. Efficacy and hepatic adverse events appeared highest with the pretomanid and rifabutin-containing regimen. Whether this is due to higher pretomanid concentrations merits exploration. Clinical trial registration available at www.
CLINICALTRIALS: gov, ID: NCT02256696.

DOI: 10.1164/rccm.202208-1475OC
PMID: 36455068

73. **Novel diaryl ether derivatives as InhA inhibitors: Design, synthesis and antimycobacterial activity.**

Bioorg Chem. 2022 Dec;129:106125. doi: 10.1016/j.bioorg.2022.106125. Epub 2022

Sep 6.

Abdelaziz OA(1), Othman DIA(2), Abdel-Aziz MM(3), Badr SMI(1), Eisa HM(1).

A new series of triclosan (TCL)-mimicking diaryl ether derivatives 7-25 were synthesized and evaluated as inhibitors of enoyl acyl carrier protein reductase InhA enzyme. In addition, these derivatives were screened as inhibitors of drug-susceptible (DS), multidrug-resistant (MDR), and extensive drug-resistant (XDR) Mycobacterium tuberculosis (MTB) strains. Most compounds exihibted superior anti-TB activities and improved ClogP compared to TCL as a standard drug. The present work has led to the identification of compounds 14, 19 and 24 which possess remarkable activities against DS, MDR and XDR MTB strains with MIC values of 1.95, 3.9 and 15.63 μg/ml, respectively for compound 14, 1.95, 3.9 and 7.81 μg/ml, respectively for compound 19 and 0.98, 1.95 and 3.9 μg/ml, respectively for compound 24. Most compounds did not exhibit toxicity to HePG2 normal cell line. Compounds 14, 19 and 24, presenting the best MIC values, were further evaluated as inhibitors of InhA enzyme. They showed high binding affinities in the micromolar range with IC50 values of 1.33, 0.6, and 0.29 μM for compounds 14, 19, and 24, respectively. Furthermore, molecular docking approach was utilized to understand the difference in bioactivities between the new compounds. In particular, the results revealed strong binding interactions and high docking scores of compounds 14, 19 and 24, which could correlate with their high activities. Mainly, the molecular modelling study of compound 24 provides an excellent platform for understanding the molecular mechanism regarding InhA inhibition. Thus, compound 24 could be a lead compound for future development of new antitubercular drugs.

DOI: 10.1016/j.bioorg.2022.106125
PMID: 36126606 [Indexed for MEDLINE]

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

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

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

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

BACKGROUND: Surgery remains an adjunctive treatment for drug-resistant tuberculosis (DR-TB) treatment failure despite the use of bedaquiline. However, there are few data about the role of surgery when combined with newer drugs. There are no outcome data from TB endemic countries, and the prognostic significance of pre-operative PET-CT remains unknown.
METHODS: We performed a prospective observational study of 57 DR-TB patients referred for surgery at Groote Schuur Hospital between 2010 and 2016. PET-CT was performed if there was nodal disease or disease outside the area of planned resection but did not influence treatment decisions. 24-month treatment success post-surgery (cure or treatment completion), including all-cause mortality, was determined.
FINDINGS: 35/57 (61.4%) patients (median age 40 years; 26% HIV-infected) underwent surgery and 22/57 (38.6%) did not (11 patients were deemed unsuitable due to bilateral cavitary disease and 11 patients declined surgery). Treatment failure was significantly lower in those who underwent surgery compared to those eligible but declined surgery [15/35 (43%) versus 11/11 (100%); relative risk 0.57 (0.42-0.76); $p < 0.01$). In patients treated with surgery, a post-operative regimen containing bedaquiline was associated with a lower odds of treatment failure [OR (95%CI) 0.06 (0.00-0.48); $p = 0.007$]. Pre-operative PET-CT ($n = 25$) did not predict treatment outcome.
INTERPRETATION: Resectional surgery for DR-TB combined with chemotherapy was associated with significantly better outcomes than chemotherapy alone. A post-operative bedaquiline-containing regimen was associated with improved outcome; however, this finding may have been confounded by higher use of bedaquiline and less loss to follow-up in the surgical group. However, PET-CT had no prognostic value. These data inform clinical practice in TB-endemic settings.
FUNDING: This work was supported by the South African MRC (RFA-EMU-02-2017) and the EDCTP (TMA-2015SF-1043 & TMA- 1051-TESAII).

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PMCID: PMC9646880
PMID: 36386040

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

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

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

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

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

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PMCID: PMC9667290
PMID: 36405997

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

76. **Complicated Case of Multidrug-Resistant Tuberculosis with Multiple Comorbidities, Successfully Treated After Several Treatment Modifications.**

Clin Med Insights Circ Respir Pulm Med. 2022 Dec 15;16:11795484221142468. doi: 10.1177/11795484221142468. eCollection 2022.

Leo B(1), Retnowulan H(2).

A 59-year-old man with relapsed pulmonary TB developed rifampin resistance. He presented with chronic untreated hepatitis B, which developed into liver cirrhosis, type 2 diabetes with diabetic retinopathy, and osteoarthritis of right knee. His initial MDR regimen included levofloxacin, cycloserine, bedaquiline, linezolid, and high-dose isoniazid. He developed episodes of linezolid-induced myelosuppression, resulting in temporary discontinuation and dose reduction, and ultimately, substitution of linezolid. On the seventh month of treatment, he developed severe depression with visual hallucination, resulting in cycloserine dose reduction. We maintained the principle of at least 4 active drugs throughout his treatment. He was considered cured after 26 months of treatment.

DOI: 10.1177/11795484221142468
PMCID: PMC9761204
PMID: 36545119

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

77. **Characterizing in vivo loss of virulence of an HN878 Mycobacterium tuberculosis**

isolate from a genetic duplication event.

Tuberculosis (Edinb). 2022 Dec;137:102272. doi: 10.1016/j.tube.2022.102272. Epub 2022 Nov 2.

Berube BJ(1), Larsen SE(2), McNeil MB(3), Reese VA(2), Pecor T(2), Kaur S(2), Parish T(4), Baldwin SL(2), Coler RN(5).

The increase of global cases of drug resistant (DR) Mycobacterium tuberculosis (M.tb) is a serious problem for the tuberculosis research community and the goals to END TB by 2030. Due to the need for advancing and screening next generation therapeutics and vaccines, we aimed to design preclinical DR models of Beijing lineage M.tb HN878 strain in different mouse backgrounds. We found escalating sensitivities of morbidity due to low dose aerosol challenge (50-100 bacilli) in CB6F1, C57BL/6 and SWR mice, respectively. We also observed that pulmonary bacterial burden at morbidity endpoints correlated inversely with survival over time between mouse strains. Interestingly, with in vitro passaging and in the process of selecting individual DR mutant colonies, we observed a significant decrease in in vivo HN878 strain virulence, which correlated with the acquisition of a large genetic duplication. We confirmed that low passage infection stocks with no or low prevalence of the duplication, including stocks directly acquired from the BEI resources biorepository, retained virulence, measured by morbidity over time. These data help confirm previous reports and emphasize the importance of monitoring virulence and stock fidelity.

DOI: 10.1016/j.tube.2022.102272
PMID: 36375278 [Indexed for MEDLINE]

78. **Current progress of functional nanobiosensors for potential tuberculosis diagnosis: The novel way for TB control?**

Front Bioeng Biotechnol. 2022 Dec 15;10:1036678. doi: 10.3389/fbioe.2022.1036678. eCollection 2022.

Yang X(1), Fan S(2)(3), Ma Y(2)(3), Chen H(1), Xu JF(2)(3), Pi J(2)(3), Wang W(1), Chen G(1).

Tuberculosis (TB), induced by the foxy Mycobacterium tuberculosis (Mtb), is still one of the top killers worldwide among infectious diseases. Although several antibiotics have been developed to significantly relieve the tuberculosis epidemics worldwide, there are still several important scientific

challenges for tuberculosis. As one of the most critical issues for tuberculosis control, the accurate and timely diagnosis of tuberculosis is critical for the following therapy of tuberculosis and thus responsible for the effective control of drug-resistant tuberculosis. Current tuberculosis diagnostic methods in clinic are still facing the difficulties that they can't provide the rapid diagnostic results with high sensitivity and accuracy, which therefore requires the development of more effective novel diagnostic strategies. In recent decades, nanomaterials have been proved to show promising potentials for novel nanobiosensor construction based on their outstanding physical, chemical and biological properties. Taking these promising advantages, nanomaterial-based biosensors show the potential to allow the rapid, sensitive and accurate tuberculosis diagnosis. Here, aiming to increase the development of more effective tuberculosis diagnostic strategy, we summarized the current progress of nanobiosensors for potential tuberculosis diagnosis application. We discussed the different kind diagnostic targets for tuberculosis diagnosis based on nanobiosensors, ranging from the detection of bacterial components from M. tuberculosis, such as DNA and proteins, to the host immunological responses, such as specific cytokine production, and to the direct whole cell detection of M. tuberculosis. We believe that this review would enhance our understandings of nanobiosensors for potential tuberculosis diagnosis, and further promote the future research on nanobiosensor-based tuberculosis diagnosis to benefit the more effective control of tuberculosis epidemic.

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PMCID: PMC9798010
PMID: 36588948

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

79. **Feasibility, Ease-of-Use, and Operational Characteristics of World Health Organization-Recommended Moderate-Complexity Automated Nucleic Acid Amplification Tests for the Detection of Tuberculosis and Resistance to Rifampicin and Isoniazid.**

J Mol Diagn. 2023 Jan;25(1):46-56. doi: 10.1016/j.jmoldx.2022.10.001. Epub 2022 Oct 13.

David A(1), de Vos M(2), Scott L(3), da Silva P(4), Trollip A(2), Ruhwald M(2), Schumacher S(2), Stevens W(5).

Four moderate-complexity automated nucleic acid amplification tests for the diagnosis of tuberculosis are reported as having laboratory analytical and clinical performance similar to that of the Cepheid Xpert MTB/RIF assay. These assays are the Abbott RealTime MTB and RealTime MTB RIF/INH Resistance, Becton Dickinson MAX MDR-TB, the Hain Lifescience/Bruker FluoroType MTBDR, and the Roche cobas MTB and MTB RIF/INH assays. The study compared feasibility, ease of use, and operational characteristics of these assays/platforms. Manufacturer input was obtained for technical characteristics. Laboratory operators were requested to complete a questionnaire on the assays' ease of use. A time-in-motion analysis was also undertaken for each platform. For ease-of-use and operational requirements, the BD MAX MDR-TB assay achieved the highest scores (86% and 90%) based on information provided by the user and manufacturer, respectively, followed by the cobas MTB and MTB-RIF/INH assay (68% and 86%), the FluoroType MTBDR assay (67% and 80%), and the Abbott RT-MTB and RT MTB RIF/INH assays (64% and 76%). The time-in-motion analysis revealed that for 94 specimens, the RealTime MTB assay required the longest processing time, followed by the cobas MTB assay and the FluoroType MTBDR assay. The BD MAX MDR-TB assay required 4.6 hours for 22 specimens. These diagnostic assays exhibited different strengths and weaknesses that should be taken into account, in addition to affordability, when considering placement of a new platform.

DOI: 10.1016/j.jmoldx.2022.10.001
PMID: 36243289 [Indexed for MEDLINE]

80. **The Subunit AEC/BC02 Vaccine Combined with Antibiotics Provides Protection in Mycobacterium tuberculosis-Infected Guinea Pigs.**

Vaccines (Basel). 2022 Dec 16;10(12):2164. doi: 10.3390/vaccines10122164.

Guo X(1)(2), Lu J(2), Li J(2), Du W(2), Shen X(2), Su C(2), Wu Y(1), Zhao A(2), Xu M(2).

A latent tuberculosis infection (LTBI) is a major source of active tuberculosis, and addressing an LTBI is crucial for the elimination of tuberculosis. The treatment of tuberculosis often requires a 6-month course of multidrug therapy, and for drug-resistant tuberculosis, a longer course of multidrug therapy is needed, which has many drawbacks. At present, vaccines are proposed as an adjunct to chemotherapy to protect populations with an LTBI and delay its recurrence. In this study, we analyzed the protective effect of a novel subunit

vaccine, AEC/BC02, in a guinea pig latent infection model. Through the optimization of different chemotherapy durations and immunization times, it was found that 4 weeks of administration of isoniazid-rifampin tablets combined with three or six injections of the vaccine could significantly reduce the gross pathological score and bacterial load in organs and improve the pathological lesions. This treatment regimen had a better protective effect than the other administration methods. Furthermore, no drug resistance of Mycobacterium tuberculosis was detected after 2 or 4 weeks of administration of the isoniazid-rifampin tablets, indicating a low risk of developing drug-resistant bacteria during short-term chemotherapy. The above results provided the foundation for an AEC/BC02 clinical protocol.

DOI: 10.3390/vaccines10122164
PMCID: PMC9781032
PMID: 36560574

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

81. **Development and Assessment of a Novel Whole-Gene-Based Targeted Next-Generation Sequencing Assay for Detecting the Susceptibility of Mycobacterium tuberculosis to 14 Drugs.**

Microbiol Spectr. 2022 Dec 21;10(6):e0260522. doi: 10.1128/spectrum.02605-22. Epub 2022 Oct 18.

Wu SH(1)(2), Xiao YX(1)(2), Hsiao HC(1)(2), Jou R(1)(2).

Targeted next-generation sequencing (tNGS) has emerged as an alternative method for detecting drug-resistant tuberculosis (DR-TB). To provide comprehensive drug susceptibility information and to address mutations missed by available commercial molecular diagnostics, we developed and evaluated a tNGS panel with 22 whole-gene targets using the Ion Torrent platform to predict drug resistance to 14 drugs, namely, rifampicin (RIF), isoniazid (INH), ethambutol (EMB), pyrazinamide (PZA), moxifloxacin (MFX), levofloxacin (LFX), amikacin (AMK), capreomycin (CM), kanamycin (KM), streptomycin (SM), bedaquiline (BDQ), clofazimine (CFZ), linezolid (LZD), and delamanid (DLM). We selected 50 and 35 Mycobacterium tuberculosis isolates with various DR profiles as the training set and the challenge set, respectively. Comparative variant analyses of the DR genes were performed using Sanger sequencing and whole-genome sequencing (WGS). Phenotypic drug susceptibility testing (pDST) results were used as gold standards. Regarding the limit of detection, the tNGS assay detected 2.9 to 3.8% minority variants in 4% mutant mixtures. The sensitivity and specificity of tNGS were 97.0% (95% confidence interval [CI] = 93.1 to 98.7%) and 99.1% (95%

CI = 97.7 to 99.7%), respectively. The concordance of tNGS with pDST was 98.5% (95% CI = 97.2 to 99.2%), which was comparable to that of WGS (98.7%, 95% CI = 97.4 to 99.3%) and better than that of Sanger sequencing (96.9%, 95% CI = 95.3 to 98.0%). The agreement between tNGS and pDST was almost perfect for RIF, INH, EMB, MFX, LFX, AMK, CM, KM, SM, BDQ, and LZD (kappa value = 0.807 to 1.000) and substantial for PZA (kappa value = 0.791). Our customized novel whole-gene-based tNGS panel is highly consistent with pDST and WGS for comprehensive and accurate prediction of drug resistance in a strengthened and streamlined DR-TB laboratory program. IMPORTANCE We developed and validated a tNGS assay that was the first to target 22 whole genes instead of regions of drug resistance genes and comprehensively detected susceptibility to 14 anti-TB drugs, with great flexibility to include new or repurposed drugs. Notably, we demonstrated that our custom-designed Ion AmpliSeq TB research panel platform had high concordance with pDST and could significantly reduce turnaround time (by approximately 70%) to meet a clinically actionable time frame. Our tNGS assay is a promising DST solution for providing needed clinical information for precision medicine-guided therapies for DR-TB and allows the rollout of active pharmacovigilance.

DOI: 10.1128/spectrum.02605-22
PMCID: PMC9769975
PMID: 36255328 [Indexed for MEDLINE]

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

82. **In Vitro Activity of the Sudapyridine (WX-081) against Non-Tuberculous Mycobacteria Isolated in Beijing, China.**

Microbiol Spectr. 2022 Dec 21;10(6):e0137222. doi: 10.1128/spectrum.01372-22. Epub 2022 Oct 17.

Zhu R(#)(1), Shang Y(#)(1)(2), Chen S(#)(1), Xiao H(1), Ren R(1), Wang F(1), Xue Y(1), Li L(3), Li Y(3), Chu N(2), Huang H(1).

Sudapyridine (WX-081) is a structural analog of bedaquiline (BDQ), which shows an anti-tuberculosis activity but, unlike BDQ, did not prolong QT interval (QT) in animal model studies. This study evaluated the antimicrobial activity of this novel drug against non-tuberculous mycobacteria (NTM). Fifty reference strains of different mycobacterial species, and 132 NTM clinical isolates from four commonly isolated NTM species were recruited. The microplate alamarBlue assay was performed to determine the MIC of WX-081 and BDQ. Cytotoxicity assay was performed for both drugs using the THP-1 cells, and the minimum bactericidal concentrations (MBCs) of both drugs against the reference strains of five

selected NTM species were also determined. All the tested reference strains had MICs lower than 0.5 μg/mL, with the majority having MICs far below 0.1 μg/mL for WX-081. The epidemiological cut-offs of WX-081 ranged from 0.0156 μg/mL to 0.25 μg/mL against commonly isolated NTM, and this value was comparable with that of BDQ. The MBC/MIC ratios suggest a bacteriostatic activity for both drugs against the five selected NTM species. Cytotoxicity assays indicated that THP-1 cells had nearly 100% viability when exposed to WX-081 for 24 h below 4 μg/mL, 200- to 300-fold the MICs of Mycobacterium intracellulare, Mycobacterium avium, and Mycobacterium kansasii. WX-081 has a strong antimicrobial activity against different NTM species with low cytotoxicity and therefore has the potential to be used for treating NTM infections. IMPORTANCE Due to the rapidly increased cases globally, non-tuberculous mycobacteria (NTM) disease has become a significant public health problem. Over 200 species or subspecies of NTM have been reported, whereas pulmonary diseases in humans are caused mainly by M. avium complex (MAC), M. kansasii, and M. abscessus. Treatment of NTM infection is often challenging as natural resistance to most antibiotics is quite common among different NTM species. Hence, identifying highly active anti-NTM agents is a priority for potent regimen establishment. The pursuit of new drugs to treat multidrug-resistant-tuberculosis (MDR-TB) may also identify some agents with strong activity against NTM. Sudapyridine (WX-081) is a structural analog of bedaquiline (BDQ), which was developed to retain the antituberculosis efficacy but eliminate the severe side effect of BDQ. This study initially evaluated the antimicrobial activity of this novel drug against non-tuberculous mycobacteria (NTM).

DOI: 10.1128/spectrum.01372-22
PMCID: PMC9769519
PMID: 36250885 [Indexed for MEDLINE]

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

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

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

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

It has been well recognized that the tumor microenvironment serves important roles in the progression and invasion of cancer. The desmoplastic reaction (DR) is a fibrous tissue reaction around tumor cells, and the prognostic significance

of DR in colorectal cancer (CRC) has been established. Tumor deposits (TD) are also an important prognostic indicator of CRC. Notably, immature type DR has been linked to poor prognosis. In addition, immature type DR is significantly associated with a higher pT stage, presence of lymphovascular invasion and lymph node metastasis; however, to the best of our knowledge, the association between DR and TD has not yet been examined. The present study aimed to clarify this association. This study included 443 consecutive patients with pT3 or pT4 CRC who underwent surgical resection. The histopathological features, including DR and TD, were evaluated. Statistical analyses of the presence of TD, DR and other clinicopathological parameters were performed. The present cohort included 205 female and 238 male patients; 293 (66.1%) and 150 (33.9%) patients were classified as pT3 and pT4, respectively. Immature, intermediate and mature DR were noted in 282 (63.7%), 91 (20.5%) and 70 patients (15.8%), respectively. TD was observed in 93 (21.0%) patients. Immature type DR was significantly associated with a higher pT stage (P<0.0001), presence of lymph node metastasis (P<0.0001), lymphatic (P=0.0007), venous (P<0.0001) and perineural invasion (P<0.0001), and higher tumor budding (TB) (P<0.0001). Moreover, immature type DR was significantly associated with the presence of TD (P<0.0001). The present study demonstrated a significant association between immature type DR and the presence of TD, and suggested a close relationship between lymphovascular invasion, DR, TB and TD. Additional studies are required to analyze the detailed mechanism underlying the development of immature DR in CRC to define novel treatment strategies.

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

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

84. J Infect. 2023 Jan;86(1):66-117. doi: 10.1016/j.jinf.2022.10.043. Epub 2022 Nov 5.

Multidrug-resistant infection in COVID-19 patients: A meta-analysis.

Hu S(1), You Y(1), Zhang S(1), Tang J(1), Chen C(1), Wen W(1), Wang C(1), Cheng Y(2), Zhou M(3), Feng Z(4), Tan T(5), Qi G(6), Wang M(7), Liu X(8).

DOI: 10.1016/j.jinf.2022.10.043
PMCID: PMC9637013

PMID: 36347426 [Indexed for MEDLINE]

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

85. **A very sneaky bug: perspectives of front-line clinicians on whole-genome sequencing for drug-resistant TB.**

Int J Tuberc Lung Dis. 2022 Dec 1;26(12):1180-1182. doi: 10.5588/ijtld.22.0335.

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DOI: 10.5588/ijtld.22.0335
PMCID: PMC9728944
PMID: 36447309 [Indexed for MEDLINE]

86. **Evaluation Study of xMAP TIER Assay on a Microsphere-Based Platform for Detecting First-Line Anti-Tuberculosis Drug Resistance.**

Int J Environ Res Public Health. 2022 Dec 19;19(24):17068. doi: 10.3390/ijerph192417068.

Ou X(1), Zhang Z(2), Zhao B(1), Song Z(1), Wang S(1), He W(1), Pei S(3), Liu D(1), Xing R(1), Xia H(1), Zhao Y(1).

Early diagnosis of drug susceptibility for tuberculosis (TB) patients could guide the timely initiation of effective treatment. We evaluated a novel multiplex xMAP TIER (Tuberculosis-Isoniazid-Ethambutol-Rifampicin) assay based on the Luminex xMAP system to detect first-line anti-tuberculous drug resistance. Deoxyribonucleic acid samples from 353 Mycobacterium tuberculosis clinical isolates were amplified by multiplex polymerase chain reaction, followed by hybridization and analysis through the xMAP system. Compared with the broth microdilution method, the sensitivity and specificity of the xMAP TIER assay for detecting resistance was 94.9% (95%CI, 90.0-99.8%) and 98.9% (95%CI,

97.7-100.0%) for rifampicin; 89.1% (95%CI, 83.9-94.3%) and 100.0% (95%CI, 100.0-100.0%) for isoniazid; 82.1% (95% CI, 68.0-96.3%) and 99.7% (95% CI, 99.0-100.0%) for ethambutol. With DNA sequencing as the reference standard, the sensitivity and specificity of xMAP TIER for detecting resistance were 95.0% (95% CI, 90.2-99.8%) and 99.6% (95% CI, 98.9-100.0%) for rifampicin; 96.9% (95% CI, 93.8-99.9%) and 100.0% (95% CI, 100.0-100.0%) for isoniazid; 86.1% (95% CI, 74.8-97.4%) and 100.0% (95% CI, 100.0-100.0%) for ethambutol. The results achieved showed that the xMAP TIER assay had good performance for detecting first-line anti-tuberculosis drug resistance, and it has the potential to diagnose drug-resistant tuberculosis more accurately due to the addition of more optimal design primers and probes on open architecture xMAP system.

DOI: 10.3390/ijerph192417068
PMCID: PMC9779588
PMID: 36554951 [Indexed for MEDLINE]

Conflict of interest statement: The authors declare no conflict of interest to this article.

87. **Cryo-EM structure of Mycobacterium tuberculosis 50S ribosomal subunit bound with clarithromycin reveals dynamic and specific interactions with macrolides.**

Emerg Microbes Infect. 2022 Dec;11(1):293-305. doi: 10.1080/22221751.2021.2022439.

Zhang W(1)(2), Li Z(3)(4), Sun Y(5), Cui P(6), Liang J(7), Xing Q(1), Wu J(6), Xu Y(1), Zhang W(6), Zhang Y(6)(8), He L(1)(9), Gao N(3).

Tuberculosis (TB) is the leading infectious disease caused by Mycobacterium tuberculosis (Mtb). Clarithromycin (CTY), an analog of erythromycin (ERY), is more potent against multidrug-resistance (MDR) TB. ERY and CTY were previously reported to bind to the nascent polypeptide exit tunnel (NPET) near peptidyl transferase center (PTC), but the only available CTY structure in complex with D. radiodurans (Dra) ribosome could be misinterpreted due to resolution limitation. To date, the mechanism of specificity and efficacy of CTY for Mtb remains elusive since the Mtb ribosome-CTY complex structure is still unknown. Here, we employed new sample preparation methods and solved the Mtb ribosome-CTY complex structure at 3.3Å with cryo-EM technique, where the crucial gate site A2062 (E. coli numbering) is located at the CTY binding site within NPET. Two alternative conformations of A2062, a novel syn-conformation as well as a swayed conformation bound with water molecule at interface, may play a role in coordinating the binding of specific drug molecules. The previously overlooked C-H hydrogen bond (H-bond) and π interaction may collectively contribute to the enhanced binding affinity. Together, our structure data provide a structural

basis for the dynamic binding as well as the specificity of CTY and explain of how a single methyl group in CTY improves its potency, which provides new evidence to reveal previously unclear mechanism of translational modulation for future drug design and anti-TB therapy. Furthermore, our sample preparation method may facilitate drug discovery based on the complexes with low water solubility drugs by cryo-EM technique.

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PMCID: PMC8786254
PMID: 34935599 [Indexed for MEDLINE]

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

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

Altern Ther Health Med. 2022 Dec 2:AT7586. Online ahead of print.

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

CONTEXT: Drug-resistant tuberculosis (TB), especially multidrug-resistant TB, has continued to increase and pan-drug-resistant TB and even fully drug-resistant TB have emerged, bringing great challenges to the treatment of TB. Development of new, safe, and effective antituberculosis drugs is an urgent need.
OBJECTIVE: The study intended to evaluate the use of the network pharmacology method to comprehensively and systematically analyze the network relationship of Kushen's main components, targets, and signaling pathways, aiming to provide new ideas and clues for an in-depth study of the mechanism of Kushen's main components in the treatment of pulmonary TB.
DESIGN: The research team performed a Network pharmacology analysis.
SETTING: The study took place in the Department of Respiratory and Critical Care Medicine at the Third People's Hospital of Yichang City in Yichang, Hubei, China.
OUTCOME MEASURES: The research team: (1) screened Kushen's active ingredients and related targets using the Traditional Chinese Medicine System Pharmacology (TCMSP) database and analysis platform; (2) used the GeneCards database and the Online Mendelian Inheritance in Man (OMIM) database to search for disease targets, (3) connected the active ingredient's targets to the disease targets to obtain predictive targets for Kushen to act against TB, (4) used the STRING database to construct a protein-protein interaction (PPI) network map, (5) used the Database for Annotation, Visualization and Integrated Discovery (DAVID) to

subject the intersecting genes to gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses, and (6) used the TCMSP and Protein Data Bank (PDB) databases to dock the active ingredients with target-protein molecules.
RESULTS: The research team found 45 active ingredients for Kushen and 177 target-protein genes related to active ingredients. The PPI network map of the Kushen-TB targets and found that the top 10 targets of Kushen were: (1) mitogen-activated protein kinase 8 (MAPK8); (2) protein kinase B (AKT1); (3) MAPK1, (4) estrogen receptor 1 (ESR1), (5) rel avian reticuloendotheliosis viral oncogene homolog A (RELA), (6) interleukin-6 (IL6), (7) MYC proto-oncogene, basic helix-loop-helix (bHLH) transcription factor MYC), (8) retinoid X receptor alpha (RXRA), (9) FOS proto-oncogene activator protein 1 (AP-1) transcription factor subunit (FOS), and (10) JUN proto-oncogene AP-1 transcription factor subunit (JUN). The KEGG analysis suggested that Kushen can intervene in TB through the hypoxia-inducible factor 1 (HIF-1) signaling pathway.
CONCLUSIONS: The network pharmacology analysis showed that Kushen's active ingredients can play a role in the treatment of TB through the HIF-1 signaling pathway.

PMID: 36455142

89. **Efficacy of steroid pulse therapy for miliary tuberculosis complicated by acute respiratory distress syndrome.**

J Clin Tuberc Other Mycobact Dis. 2022 Nov 14;29:100341. doi: 10.1016/j.jctube.2022.100341. eCollection 2022 Dec.

Wakamatsu K(1), Nagata N(2), Kumazoe H(3), Honjo S(4), Hamada M(5), Katsuki K(6), Hara M(1), Nagaoka A(1), Noda N(1), Kiyotani R(1), Fukui I(1), Ose M(1), Katahira K(1), Akasaki T(1), Maki S(1), Izumi M(1), Kawasaki M(1), Harada Y(7).

INTRODUCTION: Acute respiratory distress syndrome (ARDS) is considered a poor prognostic factor for miliary tuberculosis (MTB), but little is known about the effectiveness of steroid pulse therapy for MTB complicated by ARDS.
PATIENTS AND METHODS: Medical records were used to retrospectively investigate the prognosis and clinical information of 13 patients diagnosed with MTB complicated by ARDS among 68 patients diagnosed with MTB at our hospital between January 1994 and October 2016. None of the patients had multidrug resistant tuberculosis (TB). MTB was diagnosed by 1 radiologist and 2 respiratory physicians based on the observation of randomly distributed, uniformly sized diffuse bilateral nodules on chest computed tomography and the detection of mycobacterium TB from clinical specimens. ARDS was diagnosed based on the Berlin definition of ARDS. The effect of steroid pulse therapy on death within 3 months of hospitalization was examined using Cox proportional hazards models. Variables

were selected by the stepwise method (variable reduction method).
RESULTS: Six of 8 patients with MTB complicated by ARDS were alive 3 months after hospitalization in the steroid pulse therapy group, whereas only 1 of 5 patients was alive in the non-steroid pulse therapy group. Analysis of factors related to the survival of patients with MTB complicated by ARDS revealed that steroid pulse therapy was the strong prognostic factor (hazard ratio = 0.136 (95 % CI: 0.023-0.815)).
CONCLUSION: Our findings suggest that steroid pulse therapy improves the short-term prognosis of patients with MTB complicated by ARDS.

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PMCID: PMC9708912
PMID: 36466135

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

90. **Cost-effectiveness of 3-months isoniazid and rifapentine compared to 9-months isoniazid for latent tuberculosis infection: a systematic review.**

BMC Public Health. 2022 Dec 7;22(1):2292. doi: 10.1186/s12889-022-14766-6.

Lai WA(1), Brethour K(2), D'Silva O(3), Chaisson RE(4), Zwerling AA(3).

BACKGROUND: We conducted a systematic review examining the cost effectiveness of a 3-month course of isoniazid and rifapentine, known as 3HP, given by directly observed treatment, compared to 9 months of isoniazid that is directly observed or self-administered, for latent tuberculosis infection. 3HP has shown to be effective in reducing progression to active tuberculosis and like other short-course regimens, has higher treatment completion rates compared to standard regimens such as 9 months of isoniazid. Decision makers would benefit from knowing if the higher up-front costs of rifapentine and of the human resources needed for directly observed treatment are worth the investment for improved outcomes.
METHODS: We searched PubMed, Embase, CINAHL, LILACS, and Web of Science up to February 2022 with search concepts combining latent tuberculosis infection, directly observed treatment, and cost or cost-effectiveness. Studies included were in English or French, on human subjects, with latent tuberculosis infection, provided information on specified anti-tubercular therapy regimens, had a directly observed treatment arm, and described outcomes with some cost or economic data. We excluded posters and abstracts, treatment for multiple drug

resistant tuberculosis, and combined testing and treatment strategies. We then restricted our findings to studies examining directly-observed 3HP for comparison. The primary outcome was the cost and cost-effectiveness of directly-observed 3HP.
RESULTS: We identified 3 costing studies and 7 cost-effectiveness studies. The 3 costing studies compared directly-observed 3HP to directly-observed 9 months of isoniazid. Of the 7 cost-effectiveness studies, 4 were modelling studies based in high-income countries; one study was modelled on a high tuberculosis incidence population in the Canadian Arctic, using empiric costing data from that setting; and 2 studies were conducted in a low-income, high HIV-coinfection rate population. In five studies, directly-observed 3HP compared to self-administered isoniazid for 9 months in high-income countries, has incremental cost-effectiveness ratios that range from cost-saving to $5418 USD/QALY gained. While limited, existing evidence suggests 3HP may not be cost-effective in low-income, high HIV-coinfection settings.
CONCLUSION: Cost-effectiveness should continue to be assessed for programmatic planning and scale-up, and may vary depending on existing systems and local context, including prevalence rates and patient expectations and preferences.

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PMCID: PMC9727859
PMID: 36476206 [Indexed for MEDLINE]

Conflict of interest statement: WAL, KB, and OD have no competing interests to declare. REC has previously received consulting fees from Sanofi. Sanofi has previously donated study drugs to Johns Hopkins University. AAZ is an associate editor for BMC Infectious Diseases.

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

J Comput Aided Mol Des. 2022 Dec 22:1-12. doi: 10.1007/s10822-022-00495-w. Online ahead of print.

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

Tuberculosis (TB) is one of the main causes of death from a single pathological agent, Mycobacterium tuberculosis (Mtb). In addition, the emergence of drug-resistant TB strains has exacerbated even further the treatment outcome of

TB patients. It is thus needed the search for new therapeutic strategies to improve the current treatment and to circumvent the resistance mechanisms of Mtb. The shikimate kinase (SK) is the fifth enzyme of the shikimate pathway, which is essential for the survival of Mtb. The shikimate pathway is absent in humans, thereby indicating SK as an attractive target for the development of anti-TB drugs. In this work, a combination of in silico and in vitro techniques was used to identify potential inhibitors for SK from Mtb (MtSK). All compounds of our in-house database (Centro de Pesquisas em Biologia Molecular e Funcional, CPBMF) were submitted to in silico toxicity analysis to evaluate the risk of hepatotoxicity. Docking experiments were performed to identify the potential inhibitors of MtSK according to the predicted binding energy. In vitro inhibitory activity of MtSK-catalyzed chemical reaction at a single compound concentration was assessed. Minimum inhibitory concentration values for in vitro growth of pan-sensitive Mtb H37Rv strain were also determined. The mixed approach implemented in this work was able to identify five compounds that inhibit both MtSK and the in vitro growth of Mtb.

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PMCID: PMC9772590
PMID: 36547753

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

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

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

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

INTRODUCTION: Until 2014, there was already a significant burden of TB in Roraima, with this State being among the most affected ones in Brazil. Since 2015, though, there has been a progressive increase in cases of TB in the state of Roraima, with a notorious concentration of cases in Venezuelan migrants. Active international migration in border territories should be seen as a warning signal about the need to strengthen health surveillance and One Health actions that encompass all components involved in the risk of active transmission of diseases as tuberculosis in these scenarios.
OBJECTIVE: This study aims to analyze and compare migrants and non-migrants

notified with TB in the State of Roraima in Brazil and identify inequities in terms of diagnosis, access to treatment and outcome of the disease.
STUDY DESIGN: Quantitative, cross-sectional, descriptive study of all confirmed cases of TB notified in the Information System for Notifiable Diseases (SINAN) between 2009 and 2019.
METHODS: Data were described through counts, frequencies, prevalence ratios and 95% confidence interval. We used Poisson regression with robust variance to adjust for confounders.
RESULTS: 2111 cases of TB were reported in Roraima between 2009 and 2019 and in this study (mean age 38.2 ± 18.5 years). Cases were more frequently males, brownish race, indigenous people, with high school level education. 10.9% (n = 181) of TB cases were migrants, mainly from Venezuela (72.9%). Migrants with TB were more prone to be homeless (PR = 3.7). A higher number of cases of readmission after treatment dropout (3.3%) and AIDS diseases (11.2%) was observed among migrants compared to non-migrants. The proportion of DR-TB was higher among migrants. The percent of cure of TB was lower among migrants and the prevalence of abandonment of treatment, transfers and deaths by other causes was higher compared to non-migrants.
CONCLUSIONS: The results of the study have shown considerable differences in the epidemiological profile of TB between migrants and non-migrants living in the State of Roraima, with a tendency for poorer outcomes in the first ones as well as more concentration of vulnerabilities. These results stress out existing inequities between migrants and non-migrants with TB disease and raise questions on the health care network capacity to address these.

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PMCID: PMC9791919
PMID: 36578656

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

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

Arch Bronconeumol. 2022 Nov 30:S0300-2896(22)00642-1. doi: 10.1016/j.arbres.2022.11.013. Online ahead of print.

[Article in English, Spanish]

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

DOI: 10.1016/j.arbres.2022.11.013
PMID: 36517312

94. **A cohort study of Post COVID-19 Condition across the Beta, Delta and Omicron waves in South Africa: 6-month follow up of hospitalised and non-hospitalised participants.**

Int J Infect Dis. 2022 Dec 29:S1201-9712(22)00676-2. doi: 10.1016/j.ijid.2022.12.036. Online ahead of print.

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

OBJECTIVE: The study aimed to describe prevalence of and risk factors for Post COVID-19 Condition (PCC).
METHODS: This was a prospective, longitudinal observational cohort study. Hospitalised and non-hospitalised adults were randomly selected to undergo telephone assessment at 1, 3 and 6 months. Participants were assessed using a standardised questionnaire for evaluation of symptoms and health-related quality of life. We used negative binomial regression models to determine factors associated with the presence of ≥1 symptoms at 6 months.
RESULTS: 46.7% hospitalised and 18.5% non-hospitalised participants experienced ≥1 symptoms at 6 months (p=<0.001). Among hospitalised people living with HIV, 40.4% had persistent symptoms compared to 47.1% among HIV-uninfected participants (p=0.108). Risk factors for PCC included older age, female sex, non-black race, presence of a comorbidity, greater number of acute COVID-19 symptoms, hospitalisation/ COVID-19 severity and wave period (lower risk of persistent symptoms for Omicron compared to Beta wave). There were no associations between self-reported vaccination status with persistent symptoms.
CONCLUSION: The study revealed a high prevalence of persistent symptoms among South African participants at 6 months although decreased risk for PCC among participants infected during the Omicron BA.1 wave. These findings have serious implications for countries with resource-constrained healthcare systems.

DOI: 10.1016/j.ijid.2022.12.036
PMCID: PMC9800016

PMID: 36587841

News

1. https://www.tbonline.info/posts/2022/12/15/who-announces-landmark-changes-treatment-drug-resi/

WHO announces landmark changes in treatment of drug-resistant TB

The World Health Organization (WHO) has just released updated consolidated guidelines on the treatment of drug-resistant TB (DR-TB) featuring major improvements in treatment options for people with multidrug-resistant or rifampicin-resistant tuberculosis (MDR/RR-TB). The guidelines include a new recommendation on the use of a novel all-oral 6-month regimen composed of bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM) in people suffering from MDR/RR-TB or MDR/RR-TB with additional resistance to fluoroquinolones (pre-XDR-TB). The newly recommended BPaLM regimen offers better outcomes, remarkably shortens the duration of treatment, and thus significantly improves quality of life for people with MDR/RR-TB.

2. https://www.tballiance.org.za/news/price-reduction-paves-the-way-for-expanded-access-to-highly-effective-multidrug-resistant-tuberculosis-treatment

Price reduction paves the way for expanded access to highly effective multidrug-resistant tuberculosis treatment

Viatris, a global healthcare company, MedAccess, and TB Alliance have announced a new agreement to reduce the price of pretomanid, a drug used to treat multidrug-resistant tuberculosis, by 34%. Pretomanid is part of two new treatment regimens with high efficacy and shorter treatment durations recently recommended by the World Health Organization (WHO) as the preferred regimens for most drug-resistant tuberculosis patients.

3. **TB-PRACTECAL: Groundbreaking MSF trial finds better treatment for people with drug-resistant tuberculosis**

https://www.msf.org.za/news-and-resources/press-release/tb-practecal-groundbreaking-msf-trial-finds-better-treatment

A new all-oral, six-month treatment regimen is safer and more effective at treating multidrug-resistant tuberculosis (MDR-TB) than the current options for people with drug-resistant TB (DR-TB), according to the results of a Doctors Without Borders (MSF) study published in the New England Journal of Medicine today. These findings are a result of MSF's TB-PRACTECAL, the first-ever multi-country, randomized, controlled clinical trial to report on the efficacy and safety of a six-month, all-oral treatment regimen, which was recommended in the updated World Health Organization's (WHO) global TB treatment guidelines released last week. This

publication marks the first time TB-PRACTECAL results have been published in a peer-reviewed medical journal.

4. https://www.spotlightnsp.co.za/2022/12/06/experts-call-for-better-screening-and-treatment-of-tb-during-pregnancy/

Experts call for better screening and treatment of TB during pregnancy

Busisiwe Beko, from Khayelitsha in the Western Cape, was diagnosed with drug-resistant tuberculosis (DR-TB) while she was pregnant. She remembers it as a very difficult period in her life.“The time that I was diagnosed with TB was the time that I found out I had HIV. In that period, it was really a struggle for me, because I also found out I was pregnant. It was so unfortunate that I couldn’t produce sputum so that I could be tested for TB. That was the first challenge for me,” says Beko, who now works for Doctors Without Borders (MSF). Beko shared her experience during a session on maternal TB at the recent Union World Conference on Lung Health.