January Literature

1. **[Extensively drug-resistant tuberculosis treated with bedaquiline].**

Rev Esp Quimioter. 2023 Jan 2:lopez02jan2023. doi: 10.37201/req/073.2022. Online ahead of print.

[Article in Spanish]

López Pérez A(1), Navarro Aznarez H, Pinilla Rello A, Perales Pascual J, Arazo Garcés P.

DOI: 10.37201/req/073.2022
PMID: 36588483

2. **First and Second-Line Anti-Tuberculosis Drug-Resistance Patterns in Pulmonary Tuberculosis Patients in Zambia.**

Antibiotics (Basel). 2023 Jan 12;12(1):166. doi: 10.3390/antibiotics12010166.

Monde N(1)(2), Munyeme M(2), Chongwe G(1), Wensman JJ(3)(4), Zulu M(2)(5), Siziya S(6), Tembo R(5), Siame KK(1), Shambaba O(1)(2), Malama S(7).

BACKGROUND: Drug-resistant tuberculosis has continued to be a serious global health threat defined by complexity as well as higher morbidity and mortality wherever it occurs, Zambia included. However, the paucity of information on drug-susceptibility patterns of both first-line and second-line anti-tuberculosis (anti-TB) drugs, including the new and repurposed drugs used in the management of drug-resistant tuberculosis in Zambia, was the major thrust for conducting this study.
METHODS: A total of 132 bacteriologically confirmed TB isolates were collected from patients with pulmonary TB during the period from April 2020 to December 2021 in Southern and Eastern Provinces of Zambia. Drug-resistance profiles were determined according to four first-line and five second-line anti-TB drugs. Standard mycobacteriological methods were used to isolate and determine phenotypic drug susceptibility. Data on the participants' social-demographic characteristics were obtained using a pre-test checklist.
RESULTS: Overall, the prevalence of resistance to one or more anti-TB drugs was 23.5% (31/132, 95% CI: 16.5-31.6%). A total of 9.8% (13/132, 95% CI: 5.3-16.2%) of the patients had multidrug-resistant TB and 1.2% were new cases, while 25.5% had a history of being previously treated for TB. Among those with mono-resistant TB strains, isoniazid (INH) resistance was the highest at 9.8%

(13/132, 95% CI: 5.3-16.2%). Two (2/31) (6.5%) XDR-TB and one (1/31) (3.2%) pre-XDR-TB cases were identified among the MDR-TB patients. Previously treated patients were 40 times more likely (OR; 40.3, 95% CI: 11.1-146.5%) to have drug-resistant TB than those who had no history of being treated for TB. CONCLUSION: This study has established a high rate of multidrug-resistant TB and has further identified both pre-XDR- and XDR-TB. There is a need to intensify surveillance of MDR- and XDR-TB to inform future guidelines for effective treatment and monitoring.

DOI: 10.3390/antibiotics12010166
PMCID: PMC9855139
PMID: 36671366

Conflict of interest statement: The authors declare that there are no conflicts of interest.

3. **Cytokine upsurge among drug-resistant tuberculosis endorse the signatures of hyper inflammation and disease severity.**

Sci Rep. 2023 Jan 16;13(1):785. doi: 10.1038/s41598-023-27895-8.

Sampath P(#)(1), Rajamanickam A(#)(2), Thiruvengadam K(3), Natarajan AP(4), Hissar S(4), Dhanapal M(1), Thangavelu B(5), Jayabal L(6), Ramesh PM(7), Ranganathan UD(1), Babu S(2), Bethunaickan R(8).

Tuberculosis (TB) elimination is possible with the discovery of accurate biomarkers that define the stages of infection. Drug-resistant TB impair the current treatment strategies and worsen the unfavourable outcomes. The knowledge on host immune responses between drug-sensitive and drug-resistant infection is inadequate to understand the pathophysiological differences and disease severity. The secreted proteins, cytokines display versatile behaviour upon infection with Mycobacterium tuberculosis (MTB) and their imbalances often tend to assist disease pathology than protection. Therefore, studying these soluble proteins across TB infection spectrum (drug-resistant TB, drug-sensitive TB, and latent TB) may unveil the disease mediated responses and unique stage specific cytokine signatures. Thus, we sought to determine the plasma cytokine levels from healthy, latently infected, drug-sensitive, and drug-resistant TB individuals. Our study revealed top 8 cytokines (IL-17, IL-1α, IL-2, IL-10, IL-5, IFN-γ, TNF-α and IL-6) and their biomarker abilities to discriminate different stages of infection.

DOI: 10.1038/s41598-023-27895-8
PMCID: PMC9842614
PMID: 36646786 [Indexed for MEDLINE]

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

4. **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. 2023 Feb;127:93-105. doi: 10.1016/j.ijid.2022.11.043. Epub 2022 Dec 6.

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 [Indexed for MEDLINE]

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

5. **Population pharmacokinetics and dose evaluations of linezolid in the treatment of multidrug-resistant tuberculosis.**

Front Pharmacol. 2023 Jan 9;13:1032674. doi: 10.3389/fphar.2022.1032674. eCollection 2022.

Zhang H(1), He Y(2), Davies Forsman L(3)(4), Paues J(5)(6), Werngren J(7), Niward K(5)(6), Schön T(5)(6)(8), Bruchfeld J(3)(4), Alffenaar JW(9)(10)(11), Hu Y(1).

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Background: The pharmacokinetic/pharmacodynamics (PK/PD) target derived from the hollow-fiber system model for linezolid for treatment of the multidrug-resistant tuberculosis (MDR-TB) requires clinical validation. Therefore, this study aimed to develop a population PK model for linezolid when administered as part of a standardized treatment regimen, to identify the PK/PD threshold associated with successful treatment outcomes and to evaluate currently recommended linezolid doses. Method: This prospective multi-center cohort study of participants with laboratory-confirmed MDR-TB was conducted in five TB designated hospitals. The population PK model for linezolid was built using nonlinear mixed-effects

modeling using data from 168 participants. Boosted classification and regression tree analyses (CART) were used to identify the ratio of 0- to 24-h area under the concentration-time curve (AUC0-24h) to the minimal inhibitory concentration (MIC) threshold using the BACTEC MGIT 960 method associated with successful treatment outcome and validated in multivariate analysis using data from a different and prospective cohort of 159 participants with MDR-TB. Furthermore, based on the identified thresholds, the recommended doses were evaluated by the probability of target attainment (PTA) analysis. Result: Linezolid plasma concentrations (1008 samples) from 168 subjects treated with linezolid, were best described by a 2-compartment model with first-order absorption and elimination. An AUC0-24h/MIC > 125 was identified as a threshold for successful treatment outcome. Median time to sputum culture conversion between the group with AUC0-24h/MIC above and below 125 was 2 versus 24 months; adjusted hazard ratio (aHR), 21.7; 95% confidence interval (CI), (6.4, 72.8). The boosted CART-derived threshold and its relevance to the final treatment outcome was comparable to the previously suggested target of AUC0-24h/MIC (119) using MGIT MICs in a hollow fiber infection model. Based on the threshold from the present study, at a standard linezolid dose of 600 mg daily, PTA was simulated to achieve 100% at MGIT MICs of ≤ .25 mg which included the majority (81.1%) of isolates in the study. Conclusion: We validated an AUC0-24h/MIC threshold which may serve as a target for dose adjustment to improve efficacy of linezolid in a bedaquiline-containing treatment. Linezolid exposures with the WHO-recommended dose (600 mg daily) was sufficient for all the M. tb isolates with MIC ≤ .25 mg/L.

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PMCID: PMC9868619
PMID: 36699070

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.

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

Rev Esp Quimioter. 2023 Feb;36(1):30-44. doi: 10.37201/req/029.2022. Epub 2022 Dec 9.

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 [Indexed for MEDLINE]

7. **Rifampicin resistant Mycobacterium tuberculosis and associated factors among presumptive pulmonary tuberculosis patients in Mogadishu, Somalia.**

SAGE Open Med. 2023 Jan 10;11:20503121221148603. doi: 10.1177/20503121221148603. eCollection 2023.

Ali MM(1), Weldegebreal F(2), Kabew G(2), Urgesa K(2).

BACKGROUND: Multi-drug resistant Mycobacterium tuberculosis is a growing public health problem in developing countries including Somalia. Although, the prevalence of multi-drug resistant tuberculosis among new and retreated cases is high, data on GeneXpert- Mycobacterium tuberculosis/rifampicin-resistant assay, which is a surrogate marker for multidrug resistance, is not well explored in Mogadishu.
OBJECTIVES: To determine the prevalence of rifampicin-resistant Mycobacterium tuberculosis and its associated factors among presumptive pulmonary tuberculosis

patients visiting tuberculosis centers in Mogadishu, Somalia.
METHODS: A multicenter cross-sectional study was conducted in three tuberculosis treatment centers from March 12 to April 30, 2021. Laboratory professionals collected sputum sample consecutively from presumptive pulmonary tuberculosis participants and performed a GeneXpert assay to determine the rifampicin resistance. Socio-demographic and clinical data were collected using structured questionnaire. Logistic regression analyses were performed to assess factors associated with rifampicin resistance using an adjusted odds ratio at a 95% confidence interval. Statistical significance was considered at a p-value of less than 0.05.
RESULTS: A total of 370 presumptive tuberculosis suspects were included; of whom 58.4% were females and the mean age of the participants was 44.3 ± 14 years. Mycobacterium tuberculosis was detected in 63 (17%) (95% confidence interval = 13.2-20.8) suspects. Of these the prevalence of rifampicin-resistant Mycobacterium tuberculosis was 35% (95% confidence interval = 30.2-39.8). Anti-tuberculosis treatment history (adjusted odds ratio = 4.1; 95% confidence interval = 1.91-6.75), monthly income less than $100 USD (adjusted odds ratio = 2.2; 95% confidence interval = 1.77-5.98) and being diagnosed with Asthma (adjusted odds ratio = 2.63; 95% confidence interval = 1.3-7.3) were significantly associated with rifampicin-resistant tuberculosis.
CONCLUSION: A considerable proportion of rifampicin-resistant tuberculosis is reported in these study settings. The strong association between multidrug resistance tuberculosis and patients' retreatment history of tuberculosis, low income, and co-morbidity with asthma highlights the need for more efforts in tuberculosis treatment and monitoring programs to limit the emergence of multi-drug resistant strain in the study areas.

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PMCID: PMC9834785
PMID: 36643204

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.

8. **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.

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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.

9. **Risk factors of multidrug resistant tuberculosis among patients with tuberculosis at selected multidrug resistance treatment initiative centres in southern Ethiopia: a case-control study.**

BMJ Open. 2023 Jan 13;13(1):e061836. doi: 10.1136/bmjopen-2022-061836.

Admassu F(1), Abera E(2), Gizachew A(3), Sedoro T(3), Gari T(4).

OBJECTIVE: To identify the risk factors for multidrug resistant tuberculosis (MDR-TB) among patients with TB at selected MDR-TB treatment initiative centres, southern Ethiopia, 2021.
DESIGN: An unmatched case-control study was employed.
SETTING: Multidrug resistance treatment initiative centres in southern Ethiopia (Nigist Elen Mohamed Memorial Comprehensive Specialized Hospital and Butajira General Hospital).
PARTICIPANTS: A total sample size of 392 (79 cases and 313 controls) were selected by the systematic sampling technique. Cases were all patients with TB with culture proven or line probe assay confirmed Mycobacterium tuberculosis resistant to at least both isoniazid and rifampicin and registered on second-line TB treatment. Controls were all patients with bacteriological (molecular) proven drug-susceptible TB strains and whose recent smear results were turned to negative and registered as cured. Both bivariate and multivariable logistic regression analysis was used to identify risk factors of

MDR-TB infections.
MAIN OUTCOME MEASURE: Identifying the risk factors for MDR-TB.
RESULTS: A total of 392 participants (79 cases and 313 controls) were interviewed. Multivariable analysis showed that direct contact with known patients with TB (AOR =4.35; 95% CI: 1.45 to 9.81), history of previous TB treatment (AOR=2.51; 95% CI: 1.50 to 8.24), history of cigarette smoking (AOR=3.24; 95% CI :2.17 to 6.91) and living in rural area (AOR=4.71; 95% CI :3.13 to 9.58) were identified risk factors for MDR-TB infections.
CONCLUSIONS: The study findings revealed that direct contact with known patients with TB, previous history of TB treatment, history of cigarette smoking and rural residence were potential risk factors for the occurrence of MDR-TB. In order to reduce the burden of drug resistance, strategies of controlling MDR-TB in the study area should emphasise on enhancing public health education and reducing treatment interruptions of patients with TB and drug-resistant TB.

DOI: 10.1136/bmjopen-2022-061836
PMCID: PMC9843192
PMID: 36639214 [Indexed for MEDLINE]

Conflict of interest statement: Competing interests: None declared.

10. **Molecular Characterization of Mutations in Isoniazid- and Rifampicin-Resistant Mycobacterium tuberculosis Isolated in Thailand.**

Jpn J Infect Dis. 2023 Jan 24;76(1):39-45. doi: 10.7883/yoken.JJID.2022.055. Epub 2022 Aug 31.

Rudeeaneksin J(1), Phetsuksiri B(1), Nakajima C(2)(3), Fukushima Y(2)(3), Suthachai W(4), Tipkrua N(5), Suthum K(5), Jekloh N(6), Bunchoo S(1), Srisungngam S(1), Klayut W(1), Hamada S(7), Suzuki Y(2)(3).

The control of drug-resistant tuberculosis (TB) is a major challenge. The frequency and mutation characteristics indicate the efficiency of molecular tests for the rapid detection of TB drug resistance. This study examined the existence of katG and inhA mutations for isoniazid (INH) resistance and rpoB mutations for rifampicin (RFP) resistance. In total, 178 drug-resistant Mycobacterium tuberculosis (MTB) isolates were analyzed. Mutations in katG encoding and inhA regulatory regions were detected in 136/168 (81.0%) and 29/168 (17.3%), respectively, with the most prominent mutation of Ser315Thr substitution in katG in 126/168 (75.0%), and -15 C to T substitution in the

regulatory region of the inhA (26/168; 15.5%). Two distinct katG mutations (Tyr337Cys, 1003InsG) were identified. Of 125 RFP-resistant isolates, 118 (94.4%) carried mutations affecting the 81-bp RFP resistance-determining region, with the most commonly affected codons 450, 445, and 435 identified in 74 (59.2%), 26 (20.8%), and 12 (9.6%) isolates, respectively. Genetic mutations were highly associated with phenotypic INH and RFP resistance, and the majority shared similarities with those reported in previous studies in Thailand and other Asian countries. These data are useful for guiding the use and improvement of molecular tests for TB drug resistance.

DOI: 10.7883/yoken.JJID.2022.055
PMID: 36047179 [Indexed for MEDLINE]

11. **Missing Cases of Bacteriologically Confirmed TB/DR-TB from the National Treatment Registers in West and North Sumatra Provinces, Indonesia.**

Trop Med Infect Dis. 2023 Jan 2;8(1):31. doi: 10.3390/tropicalmed8010031.

Widoyo R(1)(2), Djafri D(2), Putri ASE(2), Yani FF(3), Kusumawati RL(4), Wongsirichot T(5), Chongsuvivatwong V(1).

This study aimed to assess the percentage of confirmed drug-sensitive (DS) TB and drug-resistant (DR) TB patients who were missing in the national treatment registration in North Sumatra and West Sumatra, where treatment services for DR-TB in North Sumatra are relatively well established compared with West Sumatra, where the system recently started. Confirmed DS/DR-TB records in the laboratory register at 40 government health facilities in 2017 and 2018 were traced to determine whether they were in the treatment register databases. A Jaro-Winkler soundexed string distance analysis enhanced by socio-demographic information matching had sensitivity and specificity over 98% in identifying the same person in the same or different databases. The laboratory data contained 5885 newly diagnosed records of bacteriologically confirmed TB cases. Of the 5885 cases, 1424 of 5353 (26.6%) DS-TB cases and 133 of 532 (25.0%) DR-TB cases were missing in the treatment notification database. The odds of missing treatment for DS-TB was similar for both provinces (AOR = 1.0 (0.9, 1.2), but for DR-TB, North Sumatra had a significantly lower missing odds ratio (AOR = 0.4 (0.2, 0.7). The system must be improved to reduce this missing rate, especially for DR-TB in West Sumatra.

DOI: 10.3390/tropicalmed8010031
PMCID: PMC9861403
PMID: 36668938

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

12. **Secondary Metabolites from Marine-Derived Bacteria with Antibiotic and Antibiofilm Activities against Drug-Resistant Pathogens.**

Mar Drugs. 2023 Jan 12;21(1):50. doi: 10.3390/md21010050.

Wibowo JT(1), Bayu A(1), Aryati WD(2), Fernandes C(3), Yanuar A(2)(4), Kijjoa A(5), Putra MY(1)(4).

The search for new antibiotics against drug-resistant microbes has been expanded to marine bacteria. Marine bacteria have been proven to be a prolific source of a myriad of novel compounds with potential biological activities. Therefore, this review highlights novel and bioactive compounds from marine bacteria reported during the period of January 2016 to December 2021. Published articles containing novel marine bacterial secondary metabolites that are active against drug-resistant pathogens were collected. Previously described compounds (prior to January 2016) are not included in this review. Unreported compounds during this period that exhibited activity against pathogenic microbes were discussed and compared in order to find the cue of the structure-bioactivity relationship. The results showed that Streptomyces are the most studied bacteria with undescribed bioactive compounds, followed by other genera in the Actinobacteria. We have categorized the structures of the compounds in the present review into four groups, based on their biosynthetic origins, as polyketide derivatives, amino acid derivatives, terpenoids, as well as compounds with mixed origin. These compounds were active against one or more drug-resistant pathogens, such as methicillin-resistant Staphylococcus aureus (MRSA), methicillin-resistant Staphylococcus epidermidis (MRSE), vancomycin-resistant Enterococci (VRE), multidrug-resistant Mycobacterium tuberculosis (MDR-TB), and amphotericin B-resistant Candida albicans. In addition, some of the compounds also showed activity against biofilm formation of the test bacteria. Some previously undescribed compounds, isolated from marine-derived bacteria during this period, could have a good potential as lead compounds for the development of drug candidates to overcome multidrug-resistant pathogens.

DOI: 10.3390/md21010050
PMCID: PMC9861457
PMID: 36662223 [Indexed for MEDLINE]

13. **Pharmacokinetic analysis of linezolid for multidrug resistant tuberculosis at a tertiary care centre in Mumbai, India.**

Front Pharmacol. 2023 Jan 4;13:1081123. doi: 10.3389/fphar.2022.1081123. eCollection 2022.

Resendiz-Galvan JE(1), Arora PR(2), Abdelwahab MT(1), Udwadia ZF(3), Rodrigues C(2), Gupta A(4)(5)(6), Denti P(1), Ashavaid TF(2), Tornheim JA(4)(5)(6).

Linezolid is an oxazolidinone used to treat multidrug-resistant tuberculosis (MDR-TB), including in the recently-endorsed shorter 6-month treatment regimens. Due to its narrow therapeutic index, linezolid is often either dose-adjusted or discontinued due to intolerance or toxicity during treatment, and the optimal balance between linezolid efficacy and toxicity remains unclear. India carries a significant burden of MDR-TB cases in the world, but limited information on the pharmacokinetics of linezolid and minimum inhibitory concentration (MIC) distribution is available from Indian MDR-TB patients. We enrolled participants from a tertiary care centre in Mumbai, India, treated for MDR-TB and receiving linezolid daily doses of 600 or 300 mg. Pharmacokinetic visits were scheduled between 1 and 15 months after treatment initiation to undergo intensive or sparse blood sampling. Linezolid concentration versus time data were analysed using non-linear mixed-effects modelling, with simulations to evaluate doses for different scenarios. We enrolled 183 participants (121 females), with a median age of 26 years (interquartile range [IQR] 21-35), weight 55.0 kg (IQR 45.6-65.8), and fat-free mass 38.7 kg (IQR 32.7-46.0). Linezolid pharmacokinetics was best described by a one-compartment model with first-order elimination allometrically scaled by fat-free mass and transit compartment absorption. The typical clearance value was 3.81 L/h. Simulations predicted that treatment with 300 mg daily achieves a high probability of target attainment (PTA) when linezolid MIC was ≤0.25 mg/L (61.5% of participant samples tested), while 600 mg daily would be required if MIC were 0.5 mg/L (29% of samples). While linezolid 300 mg daily is predicted to achieve effective targets for the majority of adults with MDR-TB, it failed to achieve the therapeutic target for 21% participants. A dose of 600 mg had a PTA >90% for all susceptible samples, but with a higher likelihood of exceeding toxicity thresholds (31% vs 9.6%). These data suggest potential benefit to individualized dosing taking host and microbial characteristics into account to improve the likelihood of treatment efficacy while minimizing risk of toxicity from linezolid for the treatment of MDR-TB. Further prospective evaluation in different clinical settings is urgently needed to inform safety and efficacy of these lower doses.

DOI: 10.3389/fphar.2022.1081123
PMCID: PMC9846493
PMID: 36686664

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.

14. **Epidemiology of tuberculosis and susceptibility to antituberculosis drugs in Reunion Island.**

BMC Infect Dis. 2023 Jan 5;23(1):4. doi: 10.1186/s12879-022-07965-4.

Loukman M(1), Olivier B(2), Vincent B(3), Rachid D(4), Cyril F(5)(6), Morgane V(1)(7), Nathalie CA(8)(9).

BACKGROUND: Tuberculosis is the first fatal infectious agent in the world with 1.2 million annual deaths for 10 million cases. Little is known about the epidemiology of tuberculosis and its resistance in Reunion Island, which is at the heart of migratory flows from highly endemic Indian Ocean territories.
METHODS: We carried out a retrospective observational study of cases of tuberculosis disease in Reunion Island between 2014 and 2018. The epidemiological, demographic, microbiological, clinical and social characteristics were analyzed from mandatory declarations, microbiology database and medical files.
RESULTS: 265 cases of tuberculosis disease were recorded over the period, ie an incidence of 6.2 / 100,000 inhabitants. 114 patients (43%) were born or resided > 6 months in the rest of the Indian Ocean area. The risk of infection was increased if birth in Madagascar (OR 23.5), Comoros (OR 8.9) or Mayotte (OR 6.8). The prevalence of HIV co-infection was low (2.5%). There were 31 cases (14.4%) of resistance to antituberculosis including 3 (1.4%) of multidrug-resistant tuberculosis and 0 case of extensively drug-resistant tuberculosis. The female gender (61.3% of resistant) was associated with resistance. The resistance rate was not significantly different depending on the geographic origin.
CONCLUSION: This is the first exhaustive epidemiological study of tuberculosis in Reunion Island. The incidence there is relatively low but increased for people with links to neighboring islands, particularly Madagascar. The prevalence of multidrug resistance is low, with no associated increased risk for patients from the Indian Ocean area.

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PMCID: PMC9814425
PMID: 36604621 [Indexed for MEDLINE]

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

15. **Examining Drug-Resistant Tuberculosis Stigma Among Health Care Workers Toward the Development of a Stigma-Reduction Intervention: Protocol for a Scoping Review.**

JMIR Res Protoc. 2023 Jan 13;12:e43084. doi: 10.2196/43084.

Aranas LL(#)(1)(2), Alam K(#)(3), Gyawali P(#)(4), Mahumud RA(#)(5).

BACKGROUND: Drug-resistant tuberculosis (DRTB) is an increasing threat to human health and economic security worldwide. Exacerbating the severity of DRTB is the low rate of service delivery, leading to increased community transmission of the disease, further amplified by stigma. Health workers are on the front line of service delivery; their efforts in all areas of disease control are suspected of having resulted in stigmatization, impacting patient-centered care. As a growing concern, attention to addressing the DRTB stigma confronting health workers is required. However, little is known about stigma among health workers delivering services to patients with DRTB. This scoping review will provide an overview that could help inform appropriate responses toward stigma-reduction interventions for these health workers.
OBJECTIVE: This scoping review protocol articulates a methodology that will examine the facets of DRTB-related stigma confronting health workers in high TB- and DRTB-burdened countries. This scoping review will (1) summarize stigma barriers and facilitators contributing to stigmatization among health workers delivering services to patients with DRTB, (2) identify the most common stigma barrier and facilitator, and (3) summarize the stigma-reduction intervention recommendations in the studies.
METHODS: Guided by Arksey and O'Malley's framework and the recommendations of Munn et al, we will conduct a scoping review of relevant literature providing evidence of DRTB-related stigma among health workers from countries with a high burden of tuberculosis (TB) and DRTB. We will search published articles written in English from 2010 onward in electronic databases using Medical Subject Headings and keywords. Our search will apply a 3-step search strategy and use software tools to manage references and facilitate the entire scoping review process. The findings of our review will be presented following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Scoping Reviews checklist. Our study is registered with Open Science Framework Registries.
RESULTS: This scoping review is part of a bigger project that will critically investigate stigma among health workers delivering services to patients resistant to TB medications. This study began in November 2021 and is expected

to finish in 2023. The study has retrieved 593 abstracts out of 12,138 articles searched since February 2022 from the identified databases. The findings of this study will be published in a peer-reviewed journal.
CONCLUSIONS: This review will provide an outline of the aspects of DRTB-related stigma confronting health workers. The findings of this review could help inform appropriate responses toward stigma-reduction interventions for these health workers. This is significant because interventions addressing related TB (and DRTB) stigma in the workplace are lacking.
INTERNATIONAL REGISTERED REPORT IDENTIFIER (IRRID): DERR1-10.2196/43084.

DOI: 10.2196/43084
PMCID: PMC9883742
PMID: 36637899

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

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

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

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

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

underwent surgery and 22/57 (38.6%) did not (11 patients were deemed unsuitable due to bilateral cavitary disease and 11 patients declined surgery). Treatment failure was significantly lower in those who underwent surgery compared to those eligible but declined surgery [15/35 (43%) versus 11/11 (100%); relative risk 0.57 (0.42-0.76); $p < 0.01$). In patients treated with surgery, a post-operative regimen containing bedaquiline was associated with a lower odds of treatment failure [OR (95%CI) 0.06 (0.00-0.48); $p = 0.007$]. Pre-operative PET-CT (n = 25) did not predict treatment outcome.
INTERPRETATION: Resectional surgery for DR-TB combined with chemotherapy was associated with significantly better outcomes than chemotherapy alone. A post-operative bedaquiline-containing regimen was associated with improved outcome; however, this finding may have been confounded by higher use of bedaquiline and less loss to follow-up in the surgical group. However, PET-CT had no prognostic value. These data inform clinical practice in TB-endemic settings.
FUNDING: This work was supported by the South African MRC (RFA-EMU-02-2017) and the EDCTP (TMA-2015SF-1043 & TMA- 1051-TESAII).

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

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

17. **Whole-genome sequencing to characterize the genetic structure and transmission risk of Mycobacterium tuberculosis in Yichang city of China.**

Front Public Health. 2023 Jan 9;10:1047965. doi: 10.3389/fpubh.2022.1047965. eCollection 2022.

Ji L(1), Tao FX(2), Yu YF(1), Liu JH(3), Yu FH(1), Bai CL(1), Wan ZY(1), Yang XB(1), Ma J(1), Zhou P(1), Niu Z(1), Zhou P(3), Xiang H(4), Chen M(5), Xiang Z(6), Zhang FQ(7), Jiang Q(2), Liu XJ(1)(3).

OBJECTIVE: The burden of both general and drug-resistant tuberculosis in rural areas is higher than that in urban areas in China. To characterize the genetic structure and transmission risk of Mycobacterium tuberculosis in rural China, we used whole genome sequencing to analyze clinical strains collected from patients in two counties of Yichang for three consecutive years.
METHODS: From 2018 to 2020, sputum samples were collected for cultures from

patients with suspected tuberculosis in Yidu and Zigui county, and DNA was extracted from the positive strains for genome sequencing. The online SAM-TB platform was used to identify the genotypes and drug resistance-related mutations of each strain, establish a phylogenetic tree, and calculated the genetic distances between pairwise strains. Twelve single nucleotide polymorphisms (SNPs) were used as thresholds to identify transmission clusters. The risk of related factors was estimated by univariable and multivariable logistic regression.
RESULTS: A total of 161 out of the collected 231 positive strains were enrolled for analysis, excluding non-tuberculous mycobacterium and duplicate strains from the same patient. These strains belonged to Lineage 2 (92, 57.1%) and Lineage 4 (69, 42.9%), respectively. A total of 49 (30.4%) strains were detected with known drug resistance-related mutations, including 6 (3.7%) multidrug-resistant-TB (MDR-TB) strains and 11 (6.8%) RIF-resistant INH-susceptible TB (Rr-TB) strains. Six of the MDR/Rr-TB (35.3%) were also resistant to fluoroquinolones, which made them pre-extensively drug-resistant TB (pre-XDR-TB). There were another seven strains with mono-resistance to fluoroquinolones and one strain with resistance to both INH and fluoroquinolones, making the overall rate of fluoroquinolones resistance 8.7% (14/161). A total of 50 strains (31.1%) were identified as transmission clusters. Patients under 45 years old (adjusted odds ratio 3.46 [95% confidential intervals 1.28-9.35]), treatment-naive patients (6.14 [1.39-27.07]) and patients infected by lineage 4 strains (2.22 [1.00-4.91]) had a higher risk of transmission.
CONCLUSION: The drug resistance of tuberculosis in rural China, especially to the second-line drug fluoroquinolones, is relatively serious. The standardized treatment for patients and the clinical use of fluoroquinolones warrant attention. At the same time, the recent transmission risk of tuberculosis is high, and rapid diagnosis and treatment management at the primary care needs to be strengthened.

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PMCID: PMC9868839
PMID: 36699912 [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.

18. **The Targeted Maximum Likelihood estimation to estimate the causal effects of the**

previous tuberculosis treatment in Multidrug-resistant tuberculosis in Sudan.

PLoS One. 2023 Jan 17;18(1):e0279976. doi: 10.1371/journal.pone.0279976. eCollection 2023.

Elduma AH(1)(2), Holakouie-Naieni K(2), Almasi-Hashiani A(3)(4), Rahimi Foroushani A(2), Mustafa Hamdan Ali H(5), Adam MAM(6), Elsony A(7), Ali Mansournia M(2).

INTRODUCTION: This study used Targeted Maximum Likelihood Estimation (TMLE) as a double robust method to estimate the causal effect of previous tuberculosis treatment history on the occurrence of multidrug-resistant tuberculosis (MDR-TB). TMLE is a method to estimate the marginal statistical parameters in case-control study design. The aim of this study was to estimate the causal effect of the previous tuberculosis treatment on the occurrence of MDR-TB using TMLE in Sudan.
METHOD: A case-control study design combined with TMLE was used to estimate parameters. Cases were MDR-TB patients and controls were and patients who cured from tuberculosis. The history of previous TB treatment was considered the main exposure, and MDR-TB as an outcome. A designed questionnaire was used to collect a set of covariates including age, time to reach a health facility, number of times stopping treatment, gender, education level, and contact with MDR-TB cases. TMLE method was used to estimate the causal association of parameters. Statistical analysis was carried out with ltmle package in R-software. Result presented in graph and tables.
RESULTS: A total number of 430 cases and 860 controls were included in this study. The estimated risk difference of the previous tuberculosis treatment was (0.189, 95% CI; 0.161, 0.218) with SE 0.014, and p-value (<0.001). In addition, the estimated risk ratio was (16.1, 95% CI; 12.932, 20.001) with SE = 0.014 and p-value (<0.001).
CONCLUSION: Our findings indicated that previous tuberculosis treatment history was determine as a risk factor for MDR-TB in Sudan. Also, TMLE method can be used to estimate the risk difference and the risk ratio in a case-control study design.

DOI: 10.1371/journal.pone.0279976
PMCID: PMC9844833
PMID: 36649340 [Indexed for MEDLINE]

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

19. **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. 2023 Jan 15;1215:123555. doi: 10.1016/j.jchromb.2022.123555. Epub 2022 Dec 9.

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.

DOI: 10.1016/j.jchromb.2022.123555
PMID: 36563654 [Indexed for MEDLINE]

Conflict of interest statement: Declaration of Competing Interest The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: 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.

20. **Genetic mutations underlying isoniazid-resistant Mycobacterium tuberculosis in Khyber Pakhtunkhwa, Pakistan.**

Tuberculosis (Edinb). 2023 Jan;138:102286. doi: 10.1016/j.tube.2022.102286. Epub 2022 Nov 28.

Khan AS(1), Phelan JE(2), Khan MT(3), Ali S(4), Qasim M(5), Mohammad N(6), Napier G(7), Ahmad S(8), Alam J(9), Khattak B(10), Campino S(11), Clark TG(12), Khan TA(13).

Tuberculosis, caused by Mycobacterium tuberculosis, is a major public health issue in Pakistan. Isoniazid is a first-line pro-drug that requires activation through an enzyme called catalase peroxidase, but is subject to widespread resistance, driven by mutations in katG and inhA genes and other loci with compensatory effects (e.g., ahpC). Here, we used whole genome sequencing data from 51 M. tuberculosis isolates collected from Khyber Pakhtunkhwa province (years 2016-2019; all isoniazid phenotypically resistant) to investigate the genetic diversity of mutations in isoniazid candidate genes. The most common mutations underlying resistance were katG S315T (37/51), fabG1 -15C>T (13/51; inhA promoter), and inhA -154G>A (7/51). Other less common mutations (n < 5) were also identified in katG (R128Q, V1A, W505*, A109T, D311G) and candidate compensatory genes ahpC (-54C>T, -51G>A) and oxyS (M249T). Using DynaMut2 software, the mutants exhibited various degrees of stability and flexibility on protein structures, with some katG mutations leading to a decrease in KatG protein flexibility. Overall, the characterisation of circulating isoniazid resistant-linked mutations will assist in drug resistant TB management and control activities in a highly endemic area of Pakistan.

DOI: 10.1016/j.tube.2022.102286

PMID: 36463715

Conflict of interest statement: Declaration of competing interest All the authors have no conflicts of interest.

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

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

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).

22. **A prospective patient registry to monitor safety, effectiveness, and utilisation of bedaquiline in patients with multidrug-resistant tuberculosis in South Korea.**

BMC Infect Dis. 2023 Jan 9;23(1):15. doi: 10.1186/s12879-022-07955-6.

Shim TS(1), Pai H(2), Mok J(3), Lee SH(4), Kwon YS(5), Choi JC(6), Park J(7), Birmingham E(8), Mao G(9), Alquier L(8), Davis K(9), Thoret-Bauchet F(10), Kim JH(11), Kim H(11), Bakare N(9).

BACKGROUND: Multidrug-resistant tuberculosis (MDR-TB) represents a major public health concern, with an ongoing need for new effective treatments. Bedaquiline is an oral diarylquinoline that has shown encouraging treatment success and culture conversion rates in MDR-TB.
METHODS: A South Korean patient registry was set up across 19 centres between 2016 and 2018 for the prospective collection of data from patients with MDR-TB who received either a bedaquiline-containing or a non-bedaquiline-containing regimen. Treatment was at the physician's discretion (bedaquiline use requiring approval by special committee) and was based on patient characteristics, disease status, and local treatment guidelines.
RESULTS: The safety population included 172 patients (88 bedaquiline and 84 non-bedaquiline). The mean (standard deviation, SD) duration of follow-up was 24.3 (9.5) months. Mean (SD) durations of treatment were 5.4 (1.8) months in

bedaquiline-treated patients and 15.7 (6.7) months in the non-bedaquiline group. Treatment success (cured and treatment completed according to WHO 2013 treatment outcome definitions) was achieved by 56.3% of bedaquiline-treated and 45.2% of non-bedaquiline-treated patients. Sputum culture conversion rates were 90.4% and 83.7% with and without bedaquiline, respectively. Diarrhoea and nausea were the most frequently reported treatment-emergent adverse events (TEAEs) in the bedaquiline group (27.3% [24/88] and 22.7% [20/88], respectively). The most frequent bedaquiline-related TEAEs were prolonged QT interval (10.2%; 9/88), and diarrhoea and nausea (9.1% each; 8/88). QT interval prolongation was reported in 19.3% (17/88) of bedaquiline-treated and 2.4% (2/84) of non-bedaquiline-treated patients, but bedaquiline was not discontinued for any patient for this reason. There were 13 (14.7%) and three (3.6%) deaths in the bedaquiline-treated and non-bedaquiline groups, respectively. Review of fatal cases revealed no unexpected safety findings, and no deaths were bedaquiline-related. The most common cause of death was worsening cancer (three patients). Patients in the bedaquiline group tended to have poorer baseline risk profiles than non-bedaquiline patients and were more likely to have relapsed or already failed second-line treatment. Interpretation of mortality data was complicated by high rates of loss to follow-up in both groups.
CONCLUSIONS: The South Korean registry findings support previous risk/benefit observations and the continued use of bedaquiline as part of combination therapy in patients with MDR-TB.

DOI: 10.1186/s12879-022-07955-6
PMCID: PMC9828359
PMID: 36624432 [Indexed for MEDLINE]

Conflict of interest statement: TSS, JHM, SHL, Y-SK, JCC and, JSP have no conflicts of interest. HP, EB, GM, LA, KD, FT-B, JHK, HK, and NB are employees of Janssen Pharmaceuticals, participating in the development of bedaquiline, and all are potential stockholders of Johnson & Johnson.

23. **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
PMCID: PMC9830532
PMID: 36243289 [Indexed for MEDLINE]

24. **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.

25. **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.

DOI: 10.1007/s00330-022-08997-9
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.

26. **Implementation challenges and lessons learned from the STREAM clinical trial-a survey of trial sites.**

Trials. 2023 Jan 23;24(1):51. doi: 10.1186/s13063-023-07068-8.

Patel LN(1), Gurumurthy M(2), Bronson G(3), Sanders K(4), Rusen ID(3).

BACKGROUND: Design and implementation of multi-country clinical trials for multidrug-resistant tuberculosis (MDR-TB) are complex for several reasons,

including trial duration, varying levels of experience and infrastructure across settings, and different regulatory requirements. STREAM was an MDR-TB clinical trial that recruited over 1000 participants. We documented challenges and best practices/lessons learned from the site perspective to improve implementation of future trials.
METHODS: We conducted a voluntary survey of trial staff at all sites to obtain information on challenges encountered and best practices/lessons learned from implementation of the STREAM trial. Respondents were asked to identify substantive aspects of trial implementation from a list that included: trial administration, laboratory strengthening/infrastructure, pharmacy and supply chain management, community engagement, regulatory and ethics requirements, health economics, and other (respondent designated) about which a practical guide would be useful to improve future trial implementation. For each aspect of trial implementation selected, respondents were asked to report challenges and best practices/lessons learned during STREAM. Lastly, respondents were asked to list up to three things they would do differently when implementing future trials. Summary statistics were generated for quantitative data and thematic analysis was undertaken for qualitative data.
RESULTS: Of 67 responses received from 13 of 15 sites, 47 (70%) were included in the analyses, after excluding duplicate or incomplete responses. Approximately half the respondents were investigators or trial coordinators. The top three aspects of trial implementation identified for a best practices/lessons learned practical guide to improve future trial implementation were: trial administration, community engagement, and laboratory strengthening/infrastructure. For both challenges and best practices/lessons learned, three common themes were identified across different aspects of trial implementation. Investment in capacity building and ongoing monitoring; investment in infrastructure and well-designed trial processes; and communication and coordination between staff and meaningful engagement of stakeholders were all thought to be critical to successful trial implementation.
CONCLUSIONS: Existing practices for clinical trial implementation should be reevaluated. Sponsors should consider the local context and the need to increase upfront investment in the cross-cutting thematic areas identified to improve trial implementation.

DOI: 10.1186/s13063-023-07068-8
PMCID: PMC9869607
PMID: 36691098 [Indexed for MEDLINE]

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

27. **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.

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

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

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

Aim: Tuberculous meningitis is an infectious disease of the central nervous system caused by Mycobacterium tuberculosis (M. tuberculosis). It mainly involves the meninges and brain parenchyma, as well as the spinal cord and meninges; Disability and mortality rates are high. In recent years, due to the increase of drug-resistant tuberculosis patients, population mobility and the prevalence of acquired immune deficiency syndrome, the incidence rate of tuberculosis has increased significantly, and tuberculous meningitis has also increased.Methods: At present, tuberculosis is still a worldwide infectious disease that seriously threatens human health, especially in underdeveloped and developing countries. China is the largest developing country in the world with a large population.Results: The situation of tuberculosis prevention and control is grim. Its disability rate is the highest in tuberculosis infection. In addition to the common non-specific manifestations, tuberculous meningoencephalitis may also have rare manifestations of stroke, hearing loss and visual loss.Conclusion: Understanding and timely improvement of corresponding examinations and targeted treatment will help improve the prognosis of patients.

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

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

29. **Successful treatment of tuberculous meningitis in an Indian female under hemodialysis therapy.**

CEN Case Rep. 2023 Jan 8. doi: 10.1007/s13730-022-00771-6. Online ahead of print.

Oshima S(1), Sakuragi M(1), Morita H(1), Oka Y(2), Tabu H(2), Marumo S(3), Suzuki H(1), Tsukamoto T(4).

Hemodialysis is a well-known risk factor for severe infection by putting patients under an immunocompromised state. Such patients are prone to opportunistic pathogen and present with atypical manifestations during infection. Tuberculous meningitis is a central nervous system infection of Mycobacterium tuberculosis, accounting for the highest mortality of all forms of tuberculosis. In fact, the mortality rate of tuberculous meningitis in hemodialysis patients is extremely poor because early clinical diagnosis is difficult. Here, we report a case of tuberculous meningitis in a 61-year-old Indian hemodialysis patient, who presented with fever of unknown origin and was successfully treated with empiric treatment with standard four-drug regimen against tuberculosis. Comprehensive screening of the origin of fever revealed only the positive results of interferon-gamma release assay, which led us to initiate an empiric therapy for tuberculosis, before making a definitive diagnosis by cerebrospinal fluid nested PCR. Soon after the initiation of the treatment, the fever immediately abated. Although the patient experienced a single episode of paradoxical worsening and severe liver injury, she recovered well without any complications. This report provides a clinical course of the disease in a hemodialysis patient, highlighting the importance of early clinical diagnosis and rapid initiation of empirical tuberculosis treatment.

DOI: 10.1007/s13730-022-00771-6
PMID: 36611090

30. **Large-scale genomic analysis of Mycobacterium tuberculosis reveals extent of target and compensatory mutations linked to multi-drug resistant tuberculosis.**

Sci Rep. 2023 Jan 12;13(1):623. doi: 10.1038/s41598-023-27516-4.

Napier G(1), Campino S(1), Phelan JE(#)(2), Clark TG(#)(3)(4).

Resistance to isoniazid (INH) and rifampicin (RIF) first-line drugs in Mycobacterium tuberculosis (Mtb), together called multi-drug resistance, threatens tuberculosis control. Resistance mutations in katG (for INH) and rpoB (RIF) genes often come with fitness costs. To overcome these costs, Mtb compensatory mutations have arisen in rpoC/rpoA (RIF) and ahpC (INH) loci. By leveraging the presence of known compensatory mutations, we aimed to detect novel resistance mutations occurring in INH and RIF target genes. Across ~ 32 k Mtb isolates with whole genome sequencing (WGS) data, there were 6262 (35.7%) with INH and 5435 (30.7%) with RIF phenotypic resistance. Known mutations in

katG and rpoB explained ~ 99% of resistance. However, 188 (0.6%) isolates had ahpC compensatory mutations with no known resistance mutations in katG, leading to the identification of 31 putative resistance mutations in katG, each observed in at least 3 isolates. These putative katG mutations can co-occur with other INH variants (e.g., katG-Ser315Thr, fabG1 mutations). For RIF, there were no isolates with rpoC/rpoA compensatory mutations and unknown resistance mutations. Overall, using WGS data we identified putative resistance markers for INH that could be used for genotypic drug-resistance profiling. Establishing the complete repertoire of Mtb resistance mutations will assist the clinical management of tuberculosis.

DOI: 10.1038/s41598-023-27516-4
PMCID: PMC9837068
PMID: 36635309 [Indexed for MEDLINE]

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

31. **Tuberculosis treatment outcomes and patient support groups, southern India.**

Bull World Health Organ. 2023 Jan 1;101(1):28-35A. doi: 10.2471/BLT.22.288237. Epub 2022 Nov 15.

Potty RS(1), Kumarasamy K(1), Munjattu JF(1), Reddy RC(2), Adepu R(3), Singarajipura A(2), Lakkappa MH(1), Swamickan R(4), Shah A(4), Panibatla V(5), Washington R(6).

OBJECTIVE: To assess treatment outcomes in tuberculosis patients participating in support group meetings in five districts of Karnataka and Telangana states in southern India.
METHODS: Tuberculosis patients from five selected districts who began treatment in 2019 were offered regular monthly support group meetings, with a focus on patients in urban slum areas with risk factors for adverse outcomes. We tracked the patients' participation in these meetings and extracted treatment outcomes from the Nikshay national tuberculosis database for the same patients in 2021. We compared treatment outcomes based on attendance of the support groups meetings.
FINDINGS: Of 30 706 tuberculosis patients who started treatment in 2019, 3651 (11.9%) attended support groups meetings. Of patients who attended at least one support meeting, 94.1% (3426/3639) had successful treatment outcomes versus 88.2% (23 745/26 922) of patients who did not attend meetings (adjusted odds ratio, aOR: 2.44; 95% confidence interval, CI: 2.10-2.82). The odds of

successful treatment outcomes were higher in meeting participants than non-participants for all variables examined including: age ≥ 60 years (aOR: 3.19; 95% CI: 2.26-4.51); female sex (aOR: 3.33; 95% CI: 2.46-4.50); diabetes comorbidity (aOR: 3.03; 95% CI: 1.91-4.81); human immunodeficiency virus infection (aOR: 3.73; 95% CI: 1.76-7.93); tuberculosis retreatment (aOR: 1.69; 1.22-2.33); and drug-resistant tuberculosis (aOR: 1.93; 95% CI: 1.21-3.09). CONCLUSION: Participation in support groups for tuberculosis patients was significantly associated with successful tuberculosis treatment outcomes, especially among high-risk groups. Expanding access to support groups could improve tuberculosis treatment outcomes at the population level.

DOI: 10.2471/BLT.22.288237
PMCID: PMC9795383
PMID: 36593787 [Indexed for MEDLINE]

32. **Correction: Gender differences among patients with drug resistant tuberculosis and HIV co-infection in Uganda: a countrywide retrospective cohort study.**

BMC Infect Dis. 2023 Jan 23;23(1):44. doi: 10.1186/s12879-023-08014-4.

Baluku JB(1)(2), Mukasa D(3), Bongomin F(4), Stadelman AM(5), Nuwagira E(6), Haller S(7), Ntabadde K(8), Turyahabwe S(9).

Erratum for
BMC Infect Dis. 2021 Oct 24;21(1):1093.

DOI: 10.1186/s12879-023-08014-4
PMCID: PMC9869599
PMID: 36690968

33. **GWAS and functional studies suggest a role for altered DNA repair in the evolution of drug resistance in Mycobacterium tuberculosis.**

Elife. 2023 Jan 25;12:e75860. doi: 10.7554/eLife.75860.

Naz S(#)(1)(2)(3), Paritosh K(#)(4), Sanyal P(1), Khan S(1), Singh Y(3), Varshney U(5), Nandicoori VK(1)(2).

The emergence of drug resistance in Mycobacterium tuberculosis (Mtb) is alarming and demands in-depth knowledge for timely diagnosis. We performed genome-wide

association analysis using 2237 clinical strains of Mtb to identify novel genetic factors that evoke drug resistance. In addition to the known direct targets, we identified for the first time, a strong association between mutations in DNA repair genes and the multidrug-resistant phenotype. To evaluate the impact of variants identified in the clinical samples in the evolution of drug resistance, we utilized knockouts and complemented strains in Mycobacterium smegmatis and Mtb. Results show that variant mutations compromised the functions of MutY and UvrB. MutY variant showed enhanced survival compared with wild-type (Rv) when the Mtb strains were subjected to multiple rounds of ex vivo antibiotic stress. In an in vivo guinea pig infection model, the MutY variant outcompeted the wild-type strain. We show that novel variant mutations in the DNA repair genes collectively compromise their functions and contribute to better survival under antibiotic/host stress conditions.

DOI: 10.7554/eLife.75860
PMCID: PMC9876569
PMID: 36695572 [Indexed for MEDLINE]

Conflict of interest statement: SN, KP, PS, SK, YS, UV, VN No competing interests declared

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

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

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

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

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

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

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

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

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

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

Early and accurate diagnosis of tuberculosis (TB) is necessary to initiate

proper therapy for the benefit of the patients and to prevent disease transmission in the community. In this study, we developed the InnowaveDX MTB/RIF (InnowaveDX) to detect Mycobacterium tuberculosis (MTB) and rifampicin resistance simultaneously. A prospective multicentre study was conducted to evaluate the diagnostic performance of InnowaveDX for the detection MTB in sputum samples as compared with Xpert and culture. The calculated limit of detection (LOD) for InnowaveDX was 9.6 CFU/ml for TB detection and 374.9 CFU/ml for RIF susceptibility. None of the other bacteria tested produced signals that fulfilled the positive TB criteria, demonstrating a species-specificity of InnowaveDX. Then 951 individuals were enrolled at 7 hospitals, of which 607 were definite TB cases with positive culture and/or Xpert results, including 354 smear-positive and 253 smear-negative cases. InnowaveDX sensitivity was 92.7% versus bacteriologically TB standard. Further follow-up revealed that 61 (91.0%) out of 67 false-positive patients with no bacteriological evidence met the criteria of clinically diagnosed TB. Among 125 RIF-resistant TB patients diagnosed by Xpert, 108 cases were correctly identified by InnowaveDX, yielding a sensitivity of 86.4%. Additionally, the proportion of very low bacterial load in the discordant susceptibility group was significantly higher than in the concordant susceptibility group (P = 0.029). To conclude, we have developed a novel molecular diagnostic with promising detection capabilities of TB and RIF susceptibility. In addition, the discordant RIF susceptibility results between InnowaveDX and Xpert are more frequently observed in samples with very low bacterial load.

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

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

36. **Nano-Delivery System of Ethanolic Extract of Propolis Targeting Mycobacterium tuberculosis via Aptamer-Modified-Niosomes.**

Nanomaterials (Basel). 2023 Jan 8;13(2):269. doi: 10.3390/nano13020269.

Sangboonruang S(1)(2), Semakul N(3), Suriyaprom S(4), Kitidee K(5), Khantipongse J(6), Intorasoot S(1)(2), Tharinjaroen CS(1)(2), Wattananandkul U(1)(2), Butr-Indr B(1)(2), Phunpae P(1)(2), Tragoolpua K(1)(2).

Tuberculosis (TB) therapy requires long-course multidrug regimens leading to the emergence of drug-resistant TB and increased public health burden worldwide. As the treatment strategy is more challenging, seeking a potent non-antibiotic

agent has been raised. Propolis serve as a natural source of bioactive molecules. It has been evidenced to eliminate various microbial pathogens including Mycobacterium tuberculosis (Mtb). In this study, we fabricated the niosome-based drug delivery platform for ethanolic extract of propolis (EEP) using thin film hydration method with Ag85A aptamer surface modification (Apt-PEGNio/EEP) to target Mtb. Physicochemical characterization of PEGNio/EEP indicated approximately -20 mV of zeta potential, 180 nm of spherical nanoparticles, 80% of entrapment efficiency, and the sustained release profile. The Apt-PEGNio/EEP and PEGNio/EEP showed no difference in these characteristics. The chemical composition in the nanostructure was confirmed by Fourier transform infrared spectrometry. Apt-PEGNio/EEP showed specific binding to Mycobacterium expressing Ag85 membrane-bound protein by confocal laser scanning microscope. It strongly inhibited Mtb in vitro and exhibited non-toxicity on alveolar macrophages. These findings indicate that the Apt-PEGNio/EEP acts as an antimycobacterial nanoparticle and might be a promising innovative targeted treatment. Further application of this smart nano-delivery system will lead to effective TB management.

DOI: 10.3390/nano13020269
PMCID: PMC9861461
PMID: 36678022

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

37. **High risk of unsuccessful treatment outcome in migrant population with tuberculosis: Data from three Italian hospitals.**

Front Public Health. 2023 Jan 10;10:1024474. doi: 10.3389/fpubh.2022.1024474. eCollection 2022.

Di Gennaro F(1), Cotugno S(1), Fasano M(2), Ricciardi A(1), Ronga L(3), Lattanzio R(1), Grimaldi A(4), Bavaro DF(1), Ciarallo M(5), Garzone S(3), De Iaco G(1), Guido G(1), Fiore JR(5), Brindicci G(1), Santoro CR(1), Sica S(5), Iacovazzi TL(2), Santantonio TA(5), Saracino A(1).

INTRODUCTION: Tuberculosis (TB) remains an unresolved global health problem and vulnerable groups such as migrants remain the most affected with a higher risk of worse outcomes. The aim of this study was to evaluate clinical features, outcomes, and adverse events in migrant and native Italian patients admitted to three Italian hospitals in Southern Italy in order to assess differences and targeted strategies.
METHODS: We performed a retrospective study on TB patients admitted between January 1, 2013, and December 31, 2021, in three Apulia hospitals. Two logistic

regression models were used, with the dependent variables being (I) unsuccessful treatment (died, loss to follow-up, and failed treatment) and (II) adverse events.
RESULTS: We enrolled 543 consecutive patients admitted at three Italian hospitals with a diagnosis of TB during the study period, of them 323 (59.5%) were migrants and 220 Italian patients. The treatment success rate in the migrant group was 44.9% (137/305), while in the non-migrant group was 97.1% (203/209). Independent factors of unsuccess treatment (death, failure or loss to follow up) were: migrant status (O.R. = 11.31; 95% CI 9.72-14.23), being male (O.R. = 4.63; 95% CI 2.16-6.10), homelessness (O.R. = 3.23; 95% CI 2.58-4.54), having a MDR (Multidrug-resistant) (O.R = 6.44; 95% CI 4.74-8.23), diagnostic delay (O.R. = 3.55; 95% CI 1.98-5.67), and length of hospitalization (O.R. = 3.43; 95% CI 1.88-5.87). While, age >65 ys (O.R. = 3.11; 95% CI 1.42-4.76), presence of extrapulmonary TB (O.R. = 1.51; 95% CI 1.31-2.18), monoresistance (O.R. = 1.45; 95% CI 1.25-3.14) and MDR pattern (O.R. = 2.44; 95% CI 1.74-5.03) resulted associated with adverse events.
CONCLUSION: Migrant population is at high risk of unsuccessful treatment (death, loss to follow-up, and treatment failure). Policies targeted specifically to this group are needed to really impact and improve their health status and also to contain the TB burden.

DOI: 10.3389/fpubh.2022.1024474
PMCID: PMC9871451
PMID: 36703820 [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.

38. **Economic evaluation of shortened, bedaquiline-containing treatment regimens for rifampicin-resistant tuberculosis (STREAM stage 2): a within-trial analysis of a randomised controlled trial.**

Lancet Glob Health. 2023 Feb;11(2):e265-e277. doi: 10.1016/S2214-109X(22)00498-3. Epub 2022 Dec 21.

Rosu L(1), Madan JJ(2), Tomeny EM(3), Muniyandi M(4), Nidoi J(5), Girma M(6), Vilc V(7), Bindroo P(8), Dhandhukiya R(9), Bayissa AK(10), Meressa D(11), Narendran G(4), Solanki R(9), Bhatnagar AK(8), Tudor E(7), Kirenga B(5),

Meredith SK(12), Nunn AJ(12), Bronson G(13), Rusen ID(13), Squire SB(3), Worrall E(3); STREAM Study Health Economic Evaluation Collaborators.

Collaborators: Ahmad S, Alexandru S, Bellenger K, Bulga TG, Cook C, Crudu V, Deborah B, Dodds W, Gebreegziabher BA, Goodall RL, Gupta P, Gurumurthy M, Langley I, Nalunjogi J, Khan S, Krishnan S, Kumar S, Lesosky M, Macari M, Makwana M, Murphy B, Murugesan RP, Patel V, Pirlog I, Rauchenberger M, Sanders K, Singh R, Subramani S, Teferi M, Tegegn NA, Velmurugan AB, Whitney J.

Erratum in
Lancet Glob Health. 2023 Feb;11(2):e196.

BACKGROUND: The STREAM stage 2 trial assessed two bedaquiline-containing regimens for rifampicin-resistant tuberculosis: a 9-month all-oral regimen and a 6-month regimen containing an injectable drug for the first 2 months. We did a within-trial economic evaluation of these regimens.
METHODS: STREAM stage 2 was an international, phase 3, non-inferiority randomised trial in which participants with rifampicin-resistant tuberculosis were randomly assigned (1:2:2:2) to the 2011 WHO regimen (terminated early), a 9-month injectable-containing regimen (control regimen), a 9-month all-oral regimen with bedaquiline (oral regimen), or a 6-month regimen with bedaquiline and an injectable for the first 2 months (6-month regimen). We prospectively collected direct and indirect costs and health-related quality of life data from trial participants until week 76 of follow-up. Cost-effectiveness of the oral and 6-month regimens versus control was estimated in four countries (oral regimen) and two countries (6-month regimen), using health-related quality of life for cost-utility analysis and trial efficacy for cost-effectiveness analysis. This trial is registered with ISRCTN, ISRCTN18148631.
FINDINGS: 300 participants were included in the economic analyses (Ethiopia, 61; India, 142; Moldova, 51; Uganda, 46). In the cost-utility analysis, the oral regimen was not cost-effective in Ethiopia, India, Moldova, and Uganda from either a provider or societal perspective. In Moldova, the oral regimen was dominant from a societal perspective. In the cost-effectiveness analysis, the oral regimen was likely to be cost-effective from a provider perspective at willingness-to-pay thresholds per additional favourable outcome of more than US$4500 in Ethiopia, $1900 in India, $3950 in Moldova, and $7900 in Uganda, and from a societal perspective at thresholds of more than $15 900 in Ethiopia, $3150 in India, and $4350 in Uganda, while in Moldova the oral regimen was dominant. In Ethiopia and India, the 6-month regimen would cost tuberculosis programmes and participants less than the control regimen and was highly likely to be cost-effective in both cost-utility analysis and cost-effectiveness analysis. Reducing the bedaquiline price from $1·81 to $1·00 per tablet made the oral regimen cost-effective in the provider-perspective cost-utility analysis in India and Moldova and dominate over the control regimen in the

provider-perspective cost-effectiveness analysis in India.
INTERPRETATION: At current costs, the oral bedaquiline-containing regimen for rifampicin-resistant tuberculosis is unlikely to be cost-effective in many low-income and middle-income countries. The 6-month regimen represents a cost-effective alternative if injectable use for 2 months is acceptable.
FUNDING: USAID and Janssen Research & Development.

DOI: 10.1016/S2214-109X(22)00498-3
PMID: 36565704 [Indexed for MEDLINE]

Conflict of interest statement: Declaration of interests LR reports consulting fees from GSK (paid to institution) and support for attending trial-related meetings from Janssen Research & Development and the US Agency for International Development (USAID; paid to institution). JJM reports support for attending meetings or travel from the Liverpool School of Tropical Medicine. EMT reports consulting fees from GSK (paid to institution) and support for attending meetings from USAID (paid to institution). MM, PB, RD, GN, AKBh, BK, SKM, AJN, GB, IDR, and EW report support for attending trial-related meetings from Janssen Research & Development and USAID (paid to institution). ET reports support for attending meetings from USAID (paid to institution). SBS reports a research grant on tuberculosis research (paid to institution) from the UK Foreign & Commonwealth Development Office, support for attending trial-related meetings from Janssen Research & Development and USAID (paid to institution), and is co-chair of the Scientific Working Group on Implementation Research for the Tropical Disease Research Foundation (unpaid). All other authors declare no competing interests.

39. **More treatment options for rifampicin-resistant tuberculosis: the role of economic evaluation in informing uptake.**

Lancet Glob Health. 2023 Feb;11(2):e183-e184. doi: 10.1016/S2214-109X(22)00519-8. Epub 2022 Dec 21.

Sweeney S(1), Singh MP(2).

DOI: 10.1016/S2214-109X(22)00519-8
PMID: 36565706 [Indexed for MEDLINE]

Conflict of interest statement: SS reports grant funding from Médecins Sans

Frontières paid to her organisation for economic evaluation work on a trial evaluating shortened regimens for multidrug-resistant and rifampicin-resistant tuberculosis; grant funding from the Bill & Melinda Gates Foundation paid to her organisation for tuberculosis modelling and analysis work; and consulting fees from WHO for support in analysis of patient cost surveys. MPS declares no competing interests.

40. **Social Support, Quality of Care, and Patient Adherence to Tuberculosis Treatment in Peru: The Mediating Role of Nurse Health Education.**

Patient Prefer Adherence. 2023 Jan 19;17:175-186. doi: 10.2147/PPA.S391930. eCollection 2023.

Dilas D(1), Flores R(1), Morales-García WC(#)(1), Calizaya-Milla YE(2), Morales-García M(3), Sairitupa-Sanchez L(4), Saintila J(#)(5).

BACKGROUND: Peru is one of the countries with the highest burden of tuberculosis (TB) and multidrug-resistant tuberculosis (MDR-TB) in the Latin American region and globally. Health education provided by nurses reinforces social support and the quality of patient care allows a greater impact on adherence to TB treatment.
PURPOSE: This study evaluated the mediating effect of treatment education between social support, quality of care, and treatment adherence in TB patients.
METHODS: A cross-sectional study was carried out considering 162 adult TB patients from four health centers of the public sector located in the center of the city of Lima, Peru. Data were collected on variables, such as social support, quality of care, health education, and adherence to TB treatment. SmartPLS was used for data analysis.
RESULTS: The results showed that social support and quality of care significantly influence health education. Likewise, health education mediates social support and quality of care for better adherence to treatment.
CONCLUSION: It is recommended that hospitals take initiatives to provide better health education on TB treatment to ensure better adherence to treatment.

DOI: 10.2147/PPA.S391930
PMCID: PMC9871033
PMID: 36704124

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

41. **The mutation rate of rpoB gene showed an upward trend with the increase of MIRU10, MIRU39 and QUB4156 repetitive number.**

BMC Genomics. 2023 Jan 16;24(1):26. doi: 10.1186/s12864-023-09120-y.

Su F(#)(1), Cao L(#)(1), Ren X(1), Hu J(1), Tavengana G(1), Wu H(2), Zhou Y(1), Fu Y(1), Jiang M(3), Wen Y(4).

BACKGROUND: Mycobacterial interspersed repetitive unit-variable number tandem repeat (MIRU-VNTR) is a frequently used typing method for identifying the Beijing genotype of Mycobacterium tuberculosis (Mtb), which is easily transformed into rifampicin (RIF) resistance. The RIF resistance of Mtb is considered to be highly related with the mutation of rpoB gene. Therefore, this study aimed to analyze the relationship between the repetitive number of MIRU loci and the mutation of rpoB gene.
METHODS: An open-source whole-genome sequencing data of Mtb was used to detect the mutation of rpoB gene and the repetitive number of MIRU loci by bioinformatics methods. Cochran-Armitage analysis was performed to analyze the trend of the rpoB gene mutation rate and the repetitive number of MIRU loci.
RESULTS: Among 357 rifampicin-resistant tuberculosis (RR-TB), 304 strains with mutated rpoB genes were detected, and 6 of 67 rifampicin susceptible strains were detected mutations. The rpoB gene mutational rate showed an upward trend with the increase of MIRU10, MIRU39, QUB4156 and MIRU16 repetitive number, but only the repetitive number of MIRU10, MRIU39 and QUB4156 were risk factors for rpoB gene mutation. The Hunter-Gaston discriminatory index (HGDI) of MIRU10 (0.65) and QUB4156 (0.62) was high in the overall sample, while MIRU39 (0.39) and MIRU16 (0.43) showed a moderate discriminatory Power.
CONCLUSION: The mutation rate of rpoB gene increases with the addition of repetitive numbers of MIRU10, QUB4156 and MIRU39 loci.

DOI: 10.1186/s12864-023-09120-y
PMCID: PMC9843906
PMID: 36646991 [Indexed for MEDLINE]

Conflict of interest statement: None declared.

42. **Regimens for Drug-Resistant Tuberculosis.**

N Engl J Med. 2023 Jan 12;388(2):190. doi: 10.1056/NEJMc2213970.

Lange C(1), Köhler N(1), Günther G(2).

Comment in
N Engl J Med. 2023 Jan 12;388(2):190-191.

Comment on
N Engl J Med. 2022 Sep 1;387(9):810-823.
N Engl J Med. 2023 Jan 12;388(2):189.

DOI: 10.1056/NEJMc2213970
PMID: 36630637 [Indexed for MEDLINE]

43. **Regimens for Drug-Resistant Tuberculosis.**

N Engl J Med. 2023 Jan 12;388(2):189. doi: 10.1056/NEJMc2213970.

Perumal R(1), Nimmo C(2), O'Donnell M(3).

Comment in
N Engl J Med. 2023 Jan 12;388(2):190.
N Engl J Med. 2023 Jan 12;388(2):190-191.

Comment on
N Engl J Med. 2022 Sep 1;387(9):810-823.

DOI: 10.1056/NEJMc2213970
PMID: 36630636 [Indexed for MEDLINE]

44. **Prevalence of pre-extensively drug-resistant tuberculosis (Pre XDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) among extra pulmonary (EP) multidrug resistant tuberculosis (MDR-TB) at a tertiary care center in Mumbai in pre Bedaquiline (BDQ) era.**

Lung India. 2023 Jan-Feb;40(1):19-23. doi: 10.4103/lungindia.lungindia_182_22.

Utpat KV(1), Rajpurohit R(1), Desai U(1).

BACKGROUND: Drug-resistant tuberculosis (DR-TB) is the most exigent and calamitous challenge encountered in treatment of TB. Extra pulmonary (EP) DR-TB poses a complex diagnostic and therapeutic challenge owing to myriad of presentations and paucibacillary nature. Data available on this subset is limited. We studied the prevalence of EPDR-TB cases among the total DR-TB cases

visiting our Programmatic management of Drug-Resistant TB (PMDT) site. We also studied the demographic and microbiological profile of these cases and analyzed the prevalence of pre-extensively drug-resistant TB (pre XDR-TB) and extensively drug-resistant TB (XDR-TB) among patients of EPDR-TB in pre Bdq era.
RESULTS: Of the 1086 DR-TB patients, 64 (5.89%) were cases of EPDR-TB. Seven out of 64 (10.93%) were primary EPDR-TB. The site wise distribution of cases was 34 (53.125%) lymph node DR-TB, 18 (28.125%) pleural DR-TB, 9 (14.0625%) spinal DR-TB/paraspinal abscess/psoas abscess, 1 case (1.5625%) each of abdominal DR-TB, sternal and gluteal abscess. On the basis of the second-line drug susceptibility testing (DST), patients were grouped into: (1) multidrug-resistant TB (MDR-TB), (2) MDR-TB with fluoroquinolone (FQ) resistance {pre XDR XDR-TB (FQ)}, (3) MDR-TB with second-line injectable (SLI) resistance {pre XDR XDR-TB (SLI)}, (4) XDR-TB. Of the 64 patients, 43 (67.185%) had MDR-TB, 19 (29.687%) had preXDR-TB (FQ), none had preXDR-TB (SLI) and 2 (3.125%) had XDR-TB. Gastro esophageal reflux disease (GERD) was the most common comorbidity seen in 26 (40.6%) patients, followed by anemia in 5 (7.8%), psychiatry problems 5 (7.8%), hypertension in 3 (4.6%), renal disorders in 2 (3.1%) while thyroid disorder, HIV and thalassemia in 1 each (1.5%).
CONCLUSION: EPDR-TB forms a small but significant proportion of total DR-TB. Lymph node DR-TB is its most common subclass. Our study emphasises the momentousness and essentiality of baseline DST to FQ and SLI in patients of DR-TB. This enables an appropriate modification of therapy at baseline itself to better the treatment outcomes. We observed a strikingly high proportion of preXDR-TB (FQ) in our study group.

DOI: 10.4103/lungindia.lungindia_182_22
PMID: 36695254

Conflict of interest statement: None

45. **Nonhydrolyzable d-phenylalanine-benzoxazole derivatives retain antitubercular activity.**

Bioorg Med Chem Lett. 2023 Jan 15;80:129116. doi: 10.1016/j.bmcl.2022.129116. Epub 2022 Dec 23.

Pepi MJ(1), Chacko S(2), Kopetz N(1), Boshoff HIM(3), Cuny GD(4), Hedstrom L(5).

The emergence of drug resistant Mycobacterium tuberculosis, the causative agent of tuberculosis, demands the development of new drugs and new drug targets. We have recently reported that the d-phenylalanine benzoxazole Q112 has potent antibacterial activity against this pathogen with a distinct mechanism of action from other antimycobacterial agents. Q112 and previously reported derivatives

were unstable in plasma and no free compound could be observed. Here we expand the structure-activity relationship for antimycobacterial activity and find nonhydrolyzable derivatives with decreased plasma binding. We also show that there is no correlation between antibacterial activity and inhibition of PanG, a putative target for these compounds.

DOI: 10.1016/j.bmcl.2022.129116
PMCID: PMC9885953
PMID: 36572353 [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.

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

Expert Rev Clin Pharmacol. 2023 Jan;16(1):5-15. doi: 10.1080/17512433.2023.2148653. Epub 2022 Nov 27.

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

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

DOI: 10.1080/17512433.2023.2148653
PMID: 36378271 [Indexed for MEDLINE]

47. **Regimens for Drug-Resistant Tuberculosis. Reply.**

N Engl J Med. 2023 Jan 12;388(2):190-191. doi: 10.1056/NEJMc2213970.

Timm J(1), Crook AM(2), Sun E(3).

Comment on
N Engl J Med. 2022 Sep 1;387(9):810-823.
N Engl J Med. 2023 Jan 12;388(2):189.
N Engl J Med. 2023 Jan 12;388(2):190.

DOI: 10.1056/NEJMc2213970
PMID: 36630638 [Indexed for MEDLINE]

48. **New treatments for Drug Resistant TB: Past imperfect, future bright.**

Lung India. 2023 Jan-Feb;40(1):1-3. doi: 10.4103/lungindia.lungindia_556_22.

Udwadia ZF(1), Patel JM(1).

DOI: 10.4103/lungindia.lungindia_556_22
PMID: 36695251

Conflict of interest statement: None

49. **[Annual progress of chemotherapy of multidrug/rifampicin-resistant tuberculosis in 2022].**

Zhonghua Jie He He Hu Xi Za Zhi. 2023 Jan 12;46(1):62-66. doi: 10.3760/cma.j.cn112147-20221030-00853.

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

Yu JJ(1), Tang SJ(1).

At present, the number of cases with multidrug/rifampicin-resistant tuberculosis (MDR/RR-TB) in China ranks fourth in the world, and the prevention and control

situation is still serious. Chemotherapy, as the most important treatment for MDR/RR-TB, was studied and explored by domestic and foreign researchers in 2022. New chemotherapeutic drugs such as delpazolid, sutezolid, telacebec and independently developed anti-tuberculosis drugs such as pyrifazimine, sudapyridine and JBD0131 are still in clinical trials. The efficacy, safety, tolerability, adverse reactions and drug resistance of bedaquiline, linezolid, delamanid and pretomanid have been studied extensively. Meanwhile, different new chemotherapy regimens centered on new drugs have been explored in-depth by international scholars. In this article, we reviewed the progress of chemotherapy of multidrug/rifampicin-resistant tuberculosis from October 2021 to September.

DOI: 10.3760/cma.j.cn112147-20221030-00853
PMID: 36617931 [Indexed for MEDLINE]

50. **Impacts of clofazimine on the treatment outcomes of drug-resistant tuberculosis.**

Microbes Infect. 2023 Jan-Feb;25(1-2):105020. doi: 10.1016/j.micinf.2022.105020. Epub 2022 Jul 3.

Wang MG(1), Liu XM(2), Wu SQ(1), He JQ(3).

BACKGROUND: The purpose of this research was to evaluate the effect of clofazimine on drug-resistant tuberculosis treatment outcomes.
METHODS: A systematic search was conducted in the PubMed, Web of Science and EMBASE databases to identify eligible studies published up to July 10, 2021. The search terms were as follows: "clofazimine," "tuberculosis," "multidrug resistant tuberculosis" or "extensively drug resistant tuberculosis" and their synonyms or similar words. Two researchers independently screened the titles, abstracts, and full texts for inclusion. Meta-analysis was performed with Stata version 16.0 (Stata Corp., College Station, Texas, USA). Risk ratios (RRs) with 95% CIs were calculated to evaluate the treatment outcome.
RESULTS: Eight studies including 3219 participants were included in the meta-analysis. The meta-analysis found that the rates of treatment completion was higher in patients receiving clofazimine-containing regimens than in those not receiving clofazimine-containing regimens (RR: 1.185 (1.060-1.325), P = 0.003). Significant reduction in treatment failure (RR: 0.598 (0.473-0.756), P < 0.001) was found in the clofazimine treatment group. The subgroup analyses of randomized controlled trials (RCTs) found a higher rates of favorable outcomes, treatment completion and cure in the clofazimine group than in the control group (RR: 1.203 (1.029-1.407), P = 0.020; RR: 3.167 (2.043-4.908), P < 0.001; and RR: 1.251 (1.031-1.518), P = 0.023, respectively). Patients receiving clofazimine had a lower risk of treatment failure than those not

receiving clofazimine (RR: 0.529 (0.454-0.616), P < 0.001). However, clofazimine treatment did not have a statistically significant effect on all-cause mortality in RCTs.
CONCLUSIONS: This study demonstrated that compared with patients who do not receive clofazimine, this drug has the potential to achieve a higher favorable outcome, treatment completion and cure rates, and a lower treatment failure risk among drug-resistant tuberculosis cases.

DOI: 10.1016/j.micinf.2022.105020
PMID: 35792202 [Indexed for MEDLINE]

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

51. **Early experience of delamanid in extensively drug-resistant pulmonary tuberculosis.**

Lung India. 2023 Jan-Feb;40(1):75-78. doi: 10.4103/lungindia.lungindia_451_22.

Marwah V(1), Patil PR(2), Choudhary R(1), Malik V(3).

Tuberculosis is a leading cause of death in our country. Multidrug-resistant tuberculosis increases the morbidity and mortality due to severe manifestations and difficult and prolonged medications. Newer antitubercular drugs like delamanid have been approved by WHO in management of these cases, but the real-world experience of this drug is lacking in our country. We present our early experience of use of delamanid in extensively drug-resistant pulmonary tuberculosis.

DOI: 10.4103/lungindia.lungindia_451_22
PMID: 36695263

Conflict of interest statement: None

52. **Analysis of drug resistance among difficult-to-treat tuberculosis patients in Ghana identifies several pre-XDR TB cases.**

Front Microbiol. 2023 Jan 12;13:1069292. doi: 10.3389/fmicb.2022.1069292.

eCollection 2022.

Otchere ID(1), Morgan PA(1), Asare P(1), Osei-Wusu S(1), Aboagye SY(2), Yirenkyi SO(3), Musah AB(1), Danso EK(1), Tetteh-Ocloo G(3), Afum T(1), Asante-Poku A(1), Laryea C(4), Poku YA(5), Bonsu F(5), Gagneux S(6), Yeboah-Manu D(1).

BACKGROUND: Resistance to tuberculosis (TB) drugs has become a major threat to global control efforts. Early case detection and drug susceptibility profiling of the infecting bacteria are essential for appropriate case management. The objective of this study was to determine the drug susceptibility profiles of difficult-to-treat (DTT) TB patients in Ghana.
METHODS: Sputum samples obtained from DTT-TB cases from health facilities across Ghana were processed for rapid diagnosis and detection of drug resistance using the Genotype MTBDRplus and Genotype MTBDRsl.v2 from Hain Life science.
RESULTS: A total of 298 (90%) out of 331 sputum samples processed gave interpretable bands out of which 175 (58.7%) were resistant to at least one drug (ANYr); 16.8% (50/298) were isoniazid-mono-resistant (INHr), 16.8% (50/298) were rifampicin-mono-resistant (RIFr), and 25.2% (75/298) were MDR. 24 (13.7%) of the ANYr were additionally resistant to at least one second line drug: 7.4% (2 RIFr, 1 INHr, and 10 MDR samples) resistant to only FQs and 2.3% (2 RIFr, 1 INHr, and 1 MDR samples) resistant to AMG drugs kanamycin (KAN), amikacin (AMK), capreomycin (CAP), and viomycin (VIO). Additionally, there were 4.0% (5 RIFr and 2 MDR samples) resistant to both FQs and AMGs. 81 (65.6%) out of 125 INH-resistant samples including INHr and MDR had katG-mutations (MT) whereas 15 (12%) had inhApro-MT. The remaining 28 (22.4%) had both katG and inhA MT. All the 19 FQ-resistant samples were gyrA mutants whereas the 10 AMGs were rrs (3), eis (3) as well as rrs, and eis co-mutants (4). Except for the seven pre-XDR samples, no sample had eis MT.
CONCLUSION: The detection of several pre-XDR TB cases in Ghana calls for intensified drug resistance surveillance and monitoring of TB patients to, respectively, ensure early diagnosis and treatment compliance.

DOI: 10.3389/fmicb.2022.1069292
PMCID: PMC9878308
PMID: 36713197

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.

53. **Host factors subverted by Mycobacterium tuberculosis: Potential targets for host directed therapy.**

Int Rev Immunol. 2023;42(1):43-70. doi: 10.1080/08830185.2021.1990277. Epub 2021 Oct 22.

Kalra R(1), Tiwari D(1), Dkhar HK(1), Bhagyaraj E(1), Kumar R(2)(3), Bhardwaj A(2)(3), Gupta P(1)(3).

INTRODUCTION: Despite new approaches in the diagnosis and treatment of tuberculosis (TB), it continues to be a major health burden. Several immunotherapies that potentiate the immune response have come up as adjuncts to drug therapies against drug resistant TB strains; however, there needs to be an urgent appraisal of host specific drug targets for improving their clinical management and to curtail disease progression. Presently, various host directed therapies (HDTs) exist (repurposed drugs, nutraceuticals, monoclonal antibodies and immunomodulatory agents), but these mostly address molecules that combat disease progression.
AREAS COVERED: The current review discusses major Mycobacterium tuberculosis (M. tuberculosis) survival paradigms inside the host and presents a plethora of host targets subverted by M. tuberculosis which can be further explored for future HDTs. The host factors unique to M. tuberculosis infection (in humans) have also been identified through an in-silico interaction mapping.
EXPERT OPINION: HDTs could become the next-generation adjunct therapies in order to counter antimicrobial resistance and virulence, as well as to reduce the duration of existing TB treatments. However, current scientific efforts are largely directed toward combatants rather than host molecules co-opted by M. tuberculosis for its survival. This might drive the immune system to a hyper-inflammatory condition; therefore, we emphasize that host factors subverted by M. tuberculosis, and their subsequent neutralization, must be considered for development of better HDTs.

DOI: 10.1080/08830185.2021.1990277
PMID: 34678117 [Indexed for MEDLINE]

54. **Nanotechnology: a contemporary therapeutic approach in combating infections from multidrug-resistant bacteria.**

Arch Microbiol. 2023 Jan 11;205(2):62. doi: 10.1007/s00203-023-03404-3.

Brar B(#)(1), Marwaha S(#)(2), Poonia AK(3)(4), Koul B(5), Kajla S(6), Rajput

VD(7).

In the 20th century, the discovery of antibiotics played an essential role in the fight against infectious diseases, including meningitis, typhoid fever, pneumonia and Mycobacterium tuberculosis. The development of multidrug resistance in microflora due to improper antibiotic use created significant public health issues. Antibiotic resistance has increased at an alarming rate in the past few decades. Multidrug-resistant bacteria (superbugs) such as methicillin-resistant Staphylococcus aureus (MRSA) as well as drug-resistant tuberculosis pose serious health implications. Despite the continuous increase in resistant microbes, the discovery of novel antibiotics is constrained by the cost and complexities of discovery of drugs. The nanotechnology has given new hope in combating this problem. In the present review, recent developments in therapeutics utilizing nanotechnology for novel antimicrobial drug development are discussed. The nanoparticles of silver, gold and zinc oxide have proved to be efficient antimicrobial agents against multidrug-resistant Klebsiella, Pseudomonas, Escherichia Coli and MRSA. Using nanostructures as carriers for antimicrobial agents provides better bioavailability, less chances of sub-therapeutic drug accumulation and less drug-related toxicity. Nanophotothermal therapy using fullerene and antibody functionalized nanostructures are other strategies that can prove to be helpful.

DOI: 10.1007/s00203-023-03404-3
PMID: 36629918 [Indexed for MEDLINE]

55. **Design, synthesis and biological evaluation of alkynyl-containing maleimide derivatives for the treatment of drug-resistant tuberculosis.**

Bioorg Chem. 2023 Feb;131:106250. doi: 10.1016/j.bioorg.2022.106250. Epub 2022 Nov 15.

Li P(1), Wang B(2), Chen X(2), Lin Z(1), Li G(3), Lu Y(4), Huang H(5).

A series of alkynyl-containing maleimides with potent anti-tuberculosis (TB) activity was developed through a rigid group substitution strategy based on our previous study. Systematic optimization of the two side chains flanking the maleimide core led to new compounds with potent activity against Mycobacterium tuberculosis (MIC < 1 μg/mL) and low cytotoxicity (IC50 > 64 μg/mL). Among them, compound 29 not only possessed good activity against extensively drug-resistant

TB and favorable hepatocyte stability, but also displayed good intracellular antimycobacterial activity in macrophages. This study lays a good foundation for identifying new alkynyl-containing maleimides as promising leads for treating drug-resistant TB.

DOI: 10.1016/j.bioorg.2022.106250
PMID: 36423487 [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.

56. **MTBDRplus and MTBDRsl for simultaneous diagnosis of gastrointestinal tuberculosis and detection of first-line and second-line drug resistance.**

J Gastroenterol Hepatol. 2023 Jan 18. doi: 10.1111/jgh.16124. Online ahead of print.

Sharma K(1), Sharma M(1)(2), Sharma V(3), Sharma M(3), Parmar UPS(4), Samanta J(3), Sharma A(5), Kochhar R(3), Sinha SK(3).

BACKGROUND: Emergence of drug resistance, especially to second-line drugs, hampers tuberculosis elimination efforts. The present study evaluated MTBDRplus and MTBDRsl assays for detecting first-line and second-line drug resistance, respectively in gastrointestinal tuberculosis (GITB).
METHODS: 30 ileo-caecal biopsy specimens, processed in the Department of Microbiology between 2012-2022, that showed growth of M. tuberculosis on culture were included in the study. DNA, extracted from culture, was subjected to MTBDRplus and MTBDRsl (Hain Lifescience, GmbH, Nehren, Germany), following manufacturer's instructions. Their performance was compared against phenotypic drug susceptibility testing (pDST) and gene sequencing.
RESULTS: Out of 30 specimens, 4 (13.33%) were mono-isoniazid resistant, 4 (13.33%) were multidrug resistant, 2 (6.67%) were pre-XDR and 2 (6.67%) had mono-fluoroquinolone resistance. The results were 100% concordant with pDST and gene sequencing.
CONCLUSIONS: In the wake of growing drug resistance in all forms of extra-pulmonary tuberculosis, including GITB, MTBDRplus and MTBDRsl are reliable tools for screening of resistance to both first-line and second-line drugs.

DOI: 10.1111/jgh.16124
PMID: 36652396

57. **Determination of genetic diversity of multidrug-resistant Mycobacterium tuberculosis strains in Turkey using 15 locus MIRU-VNTR and spoligotyping methods.**

Pathog Glob Health. 2023 Feb;117(1):85-91. doi: 10.1080/20477724.2022.2084807. Epub 2022 Jun 1.

Gürer Giray B(1), Aslantürk A(2), Şimşek H(3), Özgür D(4), Kılıç S(5), Aslan G(6).

Tuberculosis (TB) remains the leading cause of deaths from infectious disease worldwide. Nowadays, the tendency of Mycobacterium tuberculosis complex (MTBC) to spread between continents due to uncontrolled migration movements shows that TB is a global health problem. The number of studies for the detection of MTBC strains' epidemiological features in areas with TB spread risk using molecular-based methods such as spoligotyping and Mycobacterial Interspersed Repetitive Unit (MIRU) Variable Number Tandem Repeats (VNTR) at the clonal level is insufficient. In this study, it was aimed to determine the phylogenetic relationships of MTBC strains at the species level by spoligotyping and 15 locus MIRU-VNTR (MIRU-VNTR15) molecular methods of 96 multidrug-resistant (MDR) MTBC strains isolated from sputum samples of patients with a preliminary diagnosis of pulmonary TB or suspected contact history those sent to National Tuberculosis Reference Laboratory from the centers that are members of the Tuberculosis Laboratory Surveillance Network. The phylogenetic relationship between 96 MDR-TB strains was investigated with the combination of bead-based spoligotyping and MIRU-VNTR15 methods on the MAGPIX® Milliplex Map device. In this study, it was determined that the T1 family is more common in our country and LAM7-TUR family is less common than the Beijing family unlike other studies. It was determined that the strains in the same cluster had different locus profiles, and there was no transmission from the same clone in the clonal typing we performed with spoligotyping and MIRU-VNTR15.

DOI: 10.1080/20477724.2022.2084807
PMCID: PMC9848327
PMID: 35642888 [Indexed for MEDLINE]

Conflict of interest statement: No potential conflict of interest was reported by the authors.

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

Drug Discov Today. 2023 Jan 24:103508. doi: 10.1016/j.drudis.2023.103508. Online ahead of print.

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

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

DOI: 10.1016/j.drudis.2023.103508
PMID: 36706830

59. **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. 2023 Jan;28(1):43-52. doi: 10.1111/tmi.13838. Epub 2022 Dec 13.

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 [Indexed for MEDLINE]

60. **Molecular Characterization of Resistance to Second-Line Anti-Mycobacterial Drugs among Clinical Isolates of Multidrug-Resistant Mycobacterium tuberculosis.**

Clin Lab. 2023 Jan 1;69(1). doi: 10.7754/Clin.Lab.2022.220211.

Habibnia S, Karami-Zarandi M, Zaker S, Ghalavand Z, Doustdar F, Eslami G, Kazemian H.

BACKGROUND: The emergence of multidrug resistance and extensively drug-resistant

tuberculosis is a serious public health crisis. Using rapid and inexpensive molecular methods such as HRM assay in the detection of second-line drugs resistance in M. tuberculosis would be helpful in the treatment and control of XDR tuberculosis cases.
METHODS: MDR-TB isolates were collected from Iranian tuberculosis laboratories. Drug susceptibility test performed via the indirect proportion method utilizing LJ Medium. Susceptibility to ciprofloxacin, ofloxacin, amikacin, kanamycin, and capreomycin, as second-line anti-tuberculosis agents were assessed. Single point mutations in gyrA, rrs and eis genes were detected via HRM assay and DNA sequencing.
RESULTS: A DST test was performed for 56 MDR isolates and at least 27 (48.2%) isolates were resistant to CIP or OFL. Also, 14 (25%), 12 (21.4%), and 15 (26.7%) isolates were resistant to capreomycin, amikacin, and kanamycin, respectively. D94G, A90V, and G88C mutations were the most frequent mutations in gyrA gene. Also, A1401G mutation was detected more than the other mutations in rrs gene.
CONCLUSIONS: The frequency of CIP/OFL and AMK/CAP/KAN-resistant TB is considerable among Iranian tuberculosis cases. HRM assay is a rapid and inexpensive test and can detect important mutation-based drug resistance in MDR-TB and XDR-TB isolates.

DOI: 10.7754/Clin.Lab.2022.220211
PMID: 36649505 [Indexed for MEDLINE]

61. **GenoType MTBDRsl for detection of second-line drugs and ethambutol resistance in multidrug-resistant Mycobacterium tuberculosis isolates at a high-throughput laboratory.**

Diagn Microbiol Infect Dis. 2023 Feb;105(2):115856. doi: 10.1016/j.diagmicrobio.2022.115856. Epub 2022 Nov 7.

Pinhata JMW(1), Brandao AP(2), Gallo JF(3), Oliveira RS(3), Ferrazoli L(3).

We assessed the performance of MTBDRsl for detection of resistance to fluoroquinolones, aminoglycosides/cyclic peptides, and ethambutol compared to BACTEC MGIT 960 by subjecting simultaneously to both tests 385 phenotypically multidrug-resistant-Mycobacterium tuberculosis isolates from Sao Paulo, Brazil. Discordances were resolved by Sanger sequencing. MTBDRsl correctly detected 99.7% of the multidrug-resistant isolates, 87.8% of the pre-XDR, and 73.9% of the XDR. The assay showed sensitivity of 86.4%, 100%, 85.2% and 76.4% for fluoroquinolones, amikacin/kanamycin, capreomycin and ethambutol, respectively. Specificity was 100% for fluoroquinolones and aminoglycosides/cyclic peptides,

and 93.6% for ethambutol. Most fluoroquinolone-discordances were due to mutations in genome regions not targeted by the MTBDRsl v. 1.0: gyrA_H70R and gyrB_R446C, D461N, D449V, and N488D. Capreomycin-resistant isolates with wild-type rrs results on MTBDRsl presented tlyA mutations. MTBDRsl presented good performance for detecting resistance to second-line drugs and ethambutol in clinical isolates. In our setting, multidrug-resistant. isolates presented mutations not targeted by the molecular assay.

DOI: 10.1016/j.diagmicrobio.2022.115856
PMID: 36446302 [Indexed for MEDLINE]

62. **Bedaquiline's Safety Profile Monitoring in India: Considerations for Future - A Systematic review.**

Curr Drug Saf. 2023 Jan 19. doi: 10.2174/1574886318666230119102506. Online ahead of print.

Thangaraju P(1), Velmurugan H(1), Ty SS(2).

BACKGROUND: Tuberculosis is still one of the top causes of infection-related death globally. Drug-resistant tuberculosis has a high mortality rate and is still a serious public health concern around the world. The appearance of multidrug-resistant and extensively drug-resistant strains of tuberculosis has increased the need for new therapeutic options against these strains. Most of the drugs used to treat them have been poorly tested and have serious negative effects. Patients with drug-resistant tuberculosis have been fighting for access to experimental medications, particularly bedaquiline.
OBJECTIVE: The study aimed to summarise the existing evidence of bedaquiline's safety on drug-resistant tuberculosis treatment outcome and look for bedaquiline-related adverse drug reactions in the Pharmacovigilance Programme of India and World Health Organisation - Uppsala Monitoring Centre database.
METHODS: We searched the PubMed database for relevant studies on the safety profile of bedaquiline used in the treatment of drug-resistant tuberculosis and bedaquiline-related adverse drug reactions in the Pharmacovigilance Programme of India and World Health Organisation - Uppsala Monitoring Centre database published up to April 25, 2022.
RESULTS: A total of 190 abstracts were identified through the Pubmed database. In a list of 157 full-text eligible articles assessed, 149 were excluded as they did not meet the inclusion criteria. The complete articles of the remaining 8 studies were further evaluated. There were 4 prospective cohorts, 2 retrospective cohorts, and 2 case series.
CONCLUSION: Pharmacovigilance and medication safety monitoring of newer

treatments, like bedaquiline, are critical for enhancing treatment support and adherence, especially among drug-resistant tuberculosis patients.

DOI: 10.2174/1574886318666230119102506
PMID: 36655524

63. **Quantifying Mycobacterium tuberculosis Transmission Dynamics Across Global Settings: A Systematic Analysis.**

Am J Epidemiol. 2023 Jan 6;192(1):133-145. doi: 10.1093/aje/kwac181.

Smith JP, Cohen T, Dowdy D, Shrestha S, Gandhi NR, Hill AN.

The degree to which individual heterogeneity in the production of secondary cases ("superspreading") affects tuberculosis (TB) transmission has not been systematically studied. We searched for population-based or surveillance studies in which whole genome sequencing was used to estimate TB transmission and in which the size distributions of putative TB transmission clusters were enumerated. We fitted cluster-size-distribution data to a negative binomial branching process model to jointly infer the transmission parameters R (the reproduction number) and the dispersion parameter, k, which quantifies the propensity of superspreading in a population (generally, lower values of k (<1.0) suggest increased heterogeneity). Of 4,796 citations identified in our initial search, 9 studies from 8 global settings met the inclusion criteria (n = 5 studies of all TB; n = 4 studies of drug-resistant TB). Estimated R values (range, 0.10-0.73) were below 1.0, consistent with declining epidemics in the included settings; estimated k values were well below 1.0 (range, 0.02-0.48), indicating the presence of substantial individual-level heterogeneity in transmission across all settings. We estimated that a minority of cases (range, 2%-31%) drive the majority (80%) of ongoing TB transmission at the population level. Identifying sources of heterogeneity and accounting for them in TB control may have a considerable impact on mitigating TB transmission.

DOI: 10.1093/aje/kwac181
PMID: 36227246 [Indexed for MEDLINE]

64. **Efficacy of Replacing Linezolid with OTB-658 in Anti-Tuberculosis Regimens in Murine Models.**

Antimicrob Agents Chemother. 2023 Jan 9:e0139922. doi: 10.1128/aac.01399-22. Online ahead of print.

Liu H(#)(1), Zhu H(#)(1), Fu L(1), Zhang W(1), Chen X(1), Wang B(1), Guo S(1), Ding Y(1), Wang N(1), Li D(1), Lu Y(1).

Linezolid (LZD) was the first oxazolidinone approved for treating drug-resistant tuberculosis. A newly approved regimen combining LZD with bedaquiline (BDQ) and pretomanid (PMD) (BPaL regimen) is the first 6-month oral regimen that is effective against multidrug- and extensively drug-resistant tuberculosis. However, LZD toxicity, primarily due to mitochondrial protein synthesis inhibition, may undermine the efficacy of LZD regimens, and oxazolidinones with higher efficacy and lower toxicity during prolonged administration are needed. OTB-658 is an oxazolidinone anti-TB candidate derived from LZD that could replace LZD in TB treatment. We previously found that OTB-658 had better anti-TB activity and safety than LZD in vitro and in vivo. In the present work, two murine TB models were used to evaluate replacing LZD with OTB-658 in LZD-containing regimens. In the C3HeB/FeJ murine model, replacing 100 mg/kg LZD with 50 mg/kg OTB-658 in the BDQ + PMD backbone significantly reduced lung and spleen CFU counts ($P < 0.05$), and there were few relapses at 8 weeks of treatment. Replacing 100 mg/kg LZD with 50 or 100 mg/kg OTB-658 in the pyrifazimine (previously called TBI-166) + BDQ backbone did not change the anti-TB efficacy and relapse rate. In BALB/c mice, replacing 100 mg/kg LZD with 100 mg/kg OTB-658 in the TBI-166 + BDQ backbone resulted in no culture-positive lungs at 4 and 8 weeks of treatment, and there were no significant differences in relapses rate between the groups. In conclusion, OTB-658 is a promising clinical candidate that could replace LZD in the BPaL or TBI-166 + BDQ + LZD regimens and should be studied further in clinical trials.

DOI: 10.1128/aac.01399-22
PMID: 36622240

65. **Solubility Enhancement and Inhalation Delivery of Cyclodextrin-Based Inclusion Complex of Delamanid for Pulmonary Tuberculosis Treatment.**

AAPS PharmSciTech. 2023 Jan 26;24(1):49. doi: 10.1208/s12249-023-02510-1.

Patil SM(1), Barji DS(1), Chavan T(1), Patel K(1), Collazo AJ(1), Prithipaul V(1), Muth A(1), Kunda NK(2).

Tuberculosis (TB) is a contiguous airborne disease caused by Mycobacterium tuberculosis (M.tb), primarily affecting the human lungs. The progression of drug-susceptible TB to drug-resistant strains, MDR-TB and XDR-TB, has become a global challenge toward eradicating TB. Conventional TB treatment involves frequent dosing and prolonged treatment regimens predominantly by an oral or invasive route, leading to treatment-related systemic adverse effects and patient's noncompliance. Pulmonary delivery is an attractive option as we could reduce dose, limit systemic side-effects, and achieve rapid onset of action. Delamanid (DLD), an antituberculosis drug, has poor aqueous solubility, and in this study, we aim to improve its solubility using cyclodextrin complexation. We screened different cyclodextrins and found that HP-β-CD resulted in a 54-fold increase in solubility compared to a 27-fold and 13-fold increase by SBE-β-CD and HP-ɣ-CD, respectively. The stability constant (265 ± 15 M-1) and complexation efficiency (8.5 × 10-4) suggest the formation of a stable inclusion complex of DLD and HP-β-CD in a 2:1 ratio. Solid-state characterization studies (DSC, PXRD, and NMR) further confirmed successful complexation of DLD in HP-β-CD. The nebulized DLD-CD complex solution showed a mass median aerodynamic diameter of 4.42 ± 0.62 μm and fine particle fraction of 82.28 ± 2.79%, suggesting deposition in the respiratory airways. In bacterial studies, minimum inhibitory concentration of DLD-CD complex was significantly reduced (four-fold) compared to free DLD in M.tb (H37Ra strain). Furthermore, accelerated stability studies confirmed that the inclusion complex was stable for 4 weeks with 90%w/w drug content. In conclusion, we increased the aqueous solubility of DLD through cyclodextrin complexation and improved its efficacy in vitro.

DOI: 10.1208/s12249-023-02510-1
PMID: 36702977 [Indexed for MEDLINE]

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

Small Methods. 2023 Jan 22:e2201322. doi: 10.1002/smtd.202201322. Online ahead of print.

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

Establishing simple, rapid, and highly sensitive molecular assays is crucial for timely diagnosis and effective treatment of drug-resistant tuberculosis.

However, current genotypic drug susceptibility testing (DST) still encounters enormous challenges including lower sensitivity than phenotypic DST and insufficient accuracy. Herein, a simple, low-cost, multiplex real-time polymerase chain reaction-based assay is established to achieve highly sensitive detection of low-abundant mutants through competitive wild-type blocking (COWTB). Analytical performance of the COWTB assay can achieve 1% or even 0.1% mutants under background of 10 000 wild-type genomes/test. Furthermore, clinical practice feasibility is evaluated to identify resistance to rifampicin (RIF), isoniazid (INH), and streptomycin (SM) on 92 actual clinical samples, its sensitivity is 93.8% for RIF and 100% for INH and SM, and specificity is 100% each for RIF, INH, and SM when using DNA sequencing as the reference standard. In comparison, the sensitivity of reverse dot blotting assay commonly used in clinics is 93.8%, 90.0%, and 84.6%, and the specificity is 96.1%, 98.6%, and 100% for RIF, INH, and SM, respectively. Importantly, the COWTB assay can also be applicable for other drug-resistant mutations and pave a promising detection strategy to fill the gap between phenotypic and genotypic DST for detecting low-abundant drug-resistant M. tuberculosis.

DOI: 10.1002/smtd.202201322
PMID: 36683186

67. **Molecular mechanism for the involvement of CYP2E1/NF-κB axis in bedaquiline-induced hepatotoxicity.**

Life Sci. 2023 Feb 15;315:121375. doi: 10.1016/j.lfs.2023.121375. Epub 2023 Jan 6.

Kotwal P(1), Khajuria P(1), Dhiman S(2), Kour D(1), Dhiman SK(3), Kumar A(1), Nandi U(4).

Bedaquiline (BDQ) is a new class of anti-tubercular (anti-TB) drugs and is currently reserved for multiple drug resistance (MDR-TB). However, after receiving fast-track approval, its clinical studies demonstrate that its treatment is associated with hepatotoxicity and labeled as 'boxed warning' by the USFDA. No data is available on BDQ to understand the mechanism for drug-induced liver injury (DILI), a severe concern for therapeutic failure/unbearable tolerated toxicities leading to drug resistance. Therefore, we performed mechanistic studies to decipher the potential of BDQ at three dose levels (80 to 320 mg/kg) upon the repeated dose administration orally using a widely used mice model for TB. Results of BDQ treatment at the highest dose level showed that substantial increase of hepatic marker enzymes (SGPT and SGOT)

in serum, oxidative stress marker levels (MDA and GSH) in hepatic tissue, and pro-inflammatory cytokine levels (TNF-α, IL-6, and IL-1β) in serum compared to control animals. Induction of liver injury situation was further evaluated by Western blotting for various protein expressions linked to oxidative stress (SOD, Nrf2, and Keap1), inflammation (NF-κB and IKKβ), apoptosis (BAX, Bcl-2, and Caspase-3) and drug metabolism enzymes (CYP3A4 and CYP2E1). The elevated plasma level of BDQ and its metabolite (N-desmethyl BDQ) were observed, corresponding to BDQ doses. Histopathological examination and SEM analysis of the liver tissue corroborate the above-mentioned findings. Overall results suggest that BDQ treatment-associated generation of its cytotoxic metabolite could act on CYP2E1/NF-kB pathway to aggravate the condition of oxidative stress, inflammation, and apoptosis in the liver and precipitating hepatotoxicity.

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PMID: 36621541

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

68. **Discovery and Mechanistic Analysis of Structurally Diverse Inhibitors of Acetyltransferase Eis among FDA-Approved Drugs.**

Biochemistry. 2023 Jan 19. doi: 10.1021/acs.biochem.2c00658. Online ahead of print.

Pang AH(1), Green KD(1), Punetha A(1), Thamban Chandrika N(1), Howard KC(1), Garneau-Tsodikova S(1), Tsodikov OV(1).

Over one and a half million people die of tuberculosis (TB) each year. Multidrug-resistant TB infections are especially dangerous, and new drugs are needed to combat them. The high cost and complexity of drug development make repositioning of drugs that are already in clinical use for other indications a potentially time- and money-saving avenue. In this study, we identified among existing drugs five compounds: azelastine, venlafaxine, chloroquine, mefloquine, and proguanil as inhibitors of acetyltransferase Eis from Mycobacterium tuberculosis, a causative agent of TB. Eis upregulation is a cause of clinically relevant resistance of TB to kanamycin, which is inactivated by Eis-catalyzed acetylation. Crystal structures of these drugs as well as chlorhexidine in complexes with Eis showed that these inhibitors were bound in the aminoglycoside binding cavity, consistent with their established modes of inhibition with

respect to kanamycin. Among three additionally synthesized compounds, a proguanil analogue, designed based on the crystal structure of the Eis-proguanil complex, was 3-fold more potent than proguanil. The crystal structures of these compounds in complexes with Eis explained their inhibitory potencies. These initial efforts in rational drug repositioning can serve as a starting point in further development of Eis inhibitors.

DOI: 10.1021/acs.biochem.2c00658
PMID: 36657084

69. **Adjunctive Intravitreal Anti-vascular Endothelial Growth Factor and Moxifloxacin Therapy in Management of Intraocular Tubercular Granulomas.**

Ocul Immunol Inflamm. 2023 Jan;31(1):158-167. doi: 10.1080/09273948.2021.2002367. Epub 2021 Dec 17.

Agarwal M(1), Gupta C(1), Mohan KV(2), Upadhyay PK(2), Dhawan A(2), Jha V(1).

PURPOSE: To report pre and post treatment levels of VEGF-A in the aqueous humour of patients with intraocular tubercular granulomas and study the effect of a combined intravitreal anti-VEGF bevacizumab and moxifloxacin therapy on their regression.
METHODS: Aqueous samples of 10 consecutive patients with intraocular tubercular granulomas obtained before and after initiating treatment were subjected to ELISA for analysing intraocular VEGF-A levels. Intravitreal injections of bevacizumab and moxifloxacin were given weekly till complete regression of these granulomas. All patients received the usual four-drug ATT and oral corticosteroids.
RESULTS: Mean baseline VEGF-A level was 1004.27±411.40 pg/ml (401.32-1688.95) that reduced significantly to 27.62±46.86 pg/ml (6.9-131.83) at the last injection. Meannumber of intravitreal injections was 3.1 (2-4). We found significant correlation of decreasing levels of aqueous VEGF-A with the clinical regression of these tubercular granulomas.
CONCLUSIONS: Intraocular TB granulomas have high levels of VEGF-A. Weekly intravitreal injections of anti-VEGF bevacizumab with moxifloxacin as an adjunct to the standard care may cause prompt regression of tubercular granulomas.
ABBREVIATIONS: TB: Tuberculosis; IOTB: Intraocular tuberculosis; VEGF: Vascular endothelial growth factor; RD: Retinal detachment; Mtb: Mycobacterium tuberculosis; ATT: Antitubercular therapy; AMD: Age-related macular degeneration; SRF: Subretinal fluid; ELISA: Enzyme immunosorbent assay; PCR: Polymerase chain reaction; ONH: Optic nerve head; MDR-TB: Multidrug-resistant tuberculosis; pg/ml: picogram/milliliter; ESR: Erythrocyte sedimentation rate; CECT: Contrast enhanced computed tomography; DNA: Deoxyribonucleic acid; RNA:

Ribonucleic acid; BSL: Biosafety level; BCVA: Best corrected visual acuity; HM: Hand movements; KP: Keratic precipitates; PSC: Posterior subcapsular cataract; PS: Posterior synechiae; CRA: Chorio-retinal atrophy; IVMP: Intravenous methyl prednisolone; OCT: Optical coherence tomography; RPE: Retinal pigment epithelium; FFA: Fundus fluorescein angiography; ICG: Indocyanine angiography; RAP: Retinal arterial proliferans.

DOI: 10.1080/09273948.2021.2002367
PMID: 34919497 [Indexed for MEDLINE]

70. **Novel 4-aminoquinolines: Synthesis, inhibition of the Mycobacterium tuberculosis enoyl-acyl carrier protein reductase, antitubercular activity, SAR, and preclinical evaluation.**

Eur J Med Chem. 2023 Jan 5;245(Pt 1):114908. doi: 10.1016/j.ejmech.2022.114908. Epub 2022 Nov 18.

Paz JD(1), Denise de Moura Sperotto N(2), Ramos AS(2), Pissinate K(2), da Silva Rodrigues Junior V(2), Abbadi BL(2), Borsoi AF(3), Rambo RS(2), Corso Minotto AC(2), da Silva Dadda A(2), Galina L(1), Macchi Hopf FS(1), Muniz MN(2), Borges Martinelli LK(2), Roth CD(2), Madeira Silva RB(2), Perelló MA(2), de Matos Czeczot A(1), Neves CE(1), Duarte LS(2), Leyser M(4), Dias de Oliveira S(5), Bizarro CV(1), Machado P(6), Basso LA(7).

Herein a series of 4-aminoquinolines were synthesized in an attempt to optimize and study the structural features related to LABIO-17 biological activity, a Mycobacterium tuberculosis NADH-dependent enoyl-acyl carrier protein reductase (MtInhA) inhibitor previously identified by a virtual-ligand-screening approach. Structure-activity relationships led to novel submicromolar inhibitors of MtInhA and potent antitubercular agents. The lead compound is 87-fold more potent as enzymatic inhibitors and 32-fold more potent against M. tuberculosis H37Rv strain in comparison with LABIO-17. These molecules were also active against multidrug-resistant strains, devoid of apparent toxicity to mammalian cells and showed favorable in vitro ADME profiles. Additionally, these compounds were active in an intracellular model of tuberculosis (TB) infection, showed no genotoxicity signals, satisfactory absorption parameters and absence of in vivo acute toxicity. Finally, treatment with selected 4-aminoquinoline for two weeks produced bacteriostatic effect in a murine model of TB. Taken together, these findings indicate that this chemical class may furnish candidates for the future development of drug-sensitive and drug-resistant tuberculosis treatments.

DOI: 10.1016/j.ejmech.2022.114908
PMID: 36435016 [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.

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

Gene. 2023 Jan 7;857:147173. doi: 10.1016/j.gene.2023.147173. Online ahead of print.

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

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

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

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.

72. **Relative bioavailability of delamanid 50 mg tablets dispersed in water in healthy adult volunteers.**

Br J Clin Pharmacol. 2023 Jan 24. doi: 10.1111/bcp.15672. Online ahead of print.

Zou Y(1), de Jager V(2), Hesseling AC(3), Diacon AH(2), Wiesner L(4), Mostert J(2), Svensson EM(1)(5), Garcia-Prats A(3)(6).

AIM: Delamanid is a novel drug to treat of drug-resistant tuberculosis, manufactured as 50 mg solid and 25 mg dispersible tablets. We evaluated the effects of dispersing the 50 mg tablet, focusing on the relative bioavailability.
METHODS: Delamanid 50 mg tablets administered dispersed versus swallowed whole, was investigated in a phase I, four-period, cross-over study. Two of three dose strengths of delamanid (25, 50 or 100 mg) were given to healthy adult participants, both in whole and dispersed forms, with seven-day washout period. Blood samples were collected over 168 hours after each dose. Delamanid and its metabolite DM-6705 were analysed with a validated liquid chromatography tandem mass spectrometry assay. The pharmacokinetics of both analytes were analysed using nonlinear mixed-effect modelling. Palatability and acceptability were determined using a standardized questionnaire.
RESULTS: Twenty-four participants completed the study. The bioavailability of dispersed tablets was estimated to be 107% of whole tablets, with 90% confidence interval of 99.7-114%, fulfilling bioequivalence criterion. The two formulations were not significantly different regarding either bioavailability or its variability. Bioavailability increased at lower doses, by 34% (26-42%) at 50 mg and by 74% (64-86%) at 25 mg, relative to 100 mg. The majority of participants (93%) found the dispersed formulation acceptable in palatability across all delamanid doses.
CONCLUSIONS: Dispersed 50 mg delamanid tablets have similar bioavailability to tablets swallowed whole in adult volunteers. This can be an option for children and other patients who cannot swallow whole tablets, improving access to treatment.

DOI: 10.1111/bcp.15672
PMID: 36692865

73. **Performance Evaluation of the BACTEC MGIT 960 System for Rifampin Drug-Susceptibility Testing of Mycobacterium tuberculosis Using the Current WHO**

Critical Concentration.

J Clin Microbiol. 2023 Jan 26;61(1):e0108622. doi: 10.1128/jcm.01086-22. Epub 2023 Jan 5.

Yu HJ(#)(1), Kim TY(#)(1), Kim G(2), Shim HJ(3), Kang OK(1), Kim S(4), Kim CK(5), Jhun BW(6), Lee NY(1), Huh HJ(1), Lee HJ(7).

The World Health Organization recently lowered the rifampin (RIF) critical concentration (CC) for drug-susceptibility testing (DST) of Mycobacterium tuberculosis complex (MTBC) using the mycobacterial growth indicator tube (MGIT) 960 system. Here, we evaluated the diagnostic performance of the MGIT system with the revised CC for determining MTBC RIF resistance with 303 clinical MTBC isolates, including 122 isolates with rpoB mutations, of which 32 had single borderline-resistance mutations, and 181 wild-type rpoB isolates. The phenotypic RIF resistance was determined via the absolute concentration method (AC) and via MGIT using both previous (1 mg/L) and revised (0.5 mg/L) CCs for the latter method. The diagnostic accuracy of each phenotypic DST (pDST) was assessed based on rpoB genotyping as the reference standard. The overall sensitivity of the AC was 95.1% (95% confidence interval [CI], 89.6 to 98.2%), while the MGIT results with previous and revised CCs were 82.0% (95% CI 74.0 to 88.3%) and 83.6% (95% CI 75.8 to 89.7%), respectively. The 32 MTBC isolates with single borderline-resistance mutations showed a wide range of MICs, and sensitivity was not significantly increased by reducing the MGIT CC. All 181 wild-type rpoB isolates were RIF-susceptible in the AC and with MGIT using the previous CC, whereas 1 isolate was misclassified as RIF-resistant with the revised CC. Our results demonstrate that the overall diagnostic performances of the MGIT DST with the revised RIF CC and previous CC were comparable. A further large-scale study is required to demonstrate the optimal RIF CC for MGIT.

DOI: 10.1128/jcm.01086-22
PMCID: PMC9879093
PMID: 36602360 [Indexed for MEDLINE]

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