February Open Access Literature

1. **Gender and Drug-Resistant Tuberculosis in Nigeria.**

Trop Med Infect Dis. 2023 Feb 6;8(2):104. doi: 10.3390/tropicalmed8020104.

Oladimeji O(1)(2), Atiba BP(3), Anyiam FE(3), Odugbemi BA(4), Afolaranmi T(2), Zoakah AI(2), Horsburgh CR(5)(6)(7).

We conducted a retrospective study of 2555 DR-TB patients admitted to treatment between 2010 and 2016 in six geopolitical zones in Nigeria. We characterized the gender distribution of DR-TB cases and the association between demographics and clinical data, such as age, treatment category, numMaber of previous TB treatment cycles, and geopolitical zone, with gender. The independent effects of being a male or female DR-TB patient were determined using bivariate and multivariate analyzes with statistical significance of $p < 0.05$ and a 95% confidence interval. Records from a total of 2555 DR-TB patients were examined for the study. A majority were male (66.9%), largest age-group was 30-39 years old (35.8%), most had MDR-TB (61.4%), were HIV-negative (76.6%), and previously treated for TB (77.1%). The southwest treatment zone had the highest proportion of DR-TB patients (36.9%), and most DR-TB diagnoses occurred in 2016 (36.9%). On bivariate analysis, age, HIV status, treatment zone, and clinical patient group in DR-TB were significantly associated with male gender. On multivariate analysis, males aged 20-29 years (AOR: 0.19, 95% CI: 0.33-0.59, $p = 0.001$) and HIV-positive males (AOR: 0.44, 95% CI: 0.33-0.59, $p = 0.001$) had lower likelihood of MDR-TB as males in the south-south treatment zone (AOR: 1.88, 95% CI: 1.23-2.85, $p = 0.03$), and being male and aged ≥60 years (AOR: 2.19, 95% CI: 1.05-4.54, $p = 0.036$) increased the probability of DR-TB. The older male population from south-southern Nigeria and women of childbearing age had lower incidence of DR-TB than men of the same age. Tailored interventions to reduce HIV and DR-TB prevalence in the general population, particularly among women of childbearing potential, and treatment support for young and older men are relevant strategies to reduce DR-TB in Nigeria.

DOI: 10.3390/tropicalmed8020104
PMCID: PMC9964483
PMID: 36828520

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

2. **Clofazimine for the treatment of tuberculosis.**

Front Pharmacol. 2023 Feb 2;14:1100488. doi: 10.3389/fphar.2023.1100488. eCollection 2023.

Stadler JAM(1)(2), Maartens G(2)(3), Meintjes G(1)(2), Wasserman S(2)(4).

Shorter (6-9 months), fully oral regimens containing new and repurposed drugs are now the first-choice option for the treatment of drug-resistant tuberculosis (DR-TB). Clofazimine, long used in the treatment of leprosy, is one such repurposed drug that has become a cornerstone of DR-TB treatment and ongoing trials are exploring novel, shorter clofazimine-containing regimens for drug-resistant as well as drug-susceptible tuberculosis. Clofazimine's repurposing was informed by evidence of potent activity against DR-TB strains in vitro and in mice and a treatment-shortening effect in DR-TB patients as part of a multidrug regimen. Clofazimine entered clinical use in the 1950s without the rigorous safety and pharmacokinetic evaluation which is part of modern drug development and current dosing is not evidence-based. Recent studies have begun to characterize clofazimine's exposure-response relationship for safety and efficacy in populations with TB. Despite being better tolerated than some other second-line TB drugs, the extent and impact of adverse effects including skin discolouration and cardiotoxicity are not well understood and together with emergent resistance, may undermine clofazimine use in DR-TB programmes. Furthermore, clofazimine's precise mechanism of action is not well established, as is the genetic basis of clofazimine resistance. In this narrative review, we present an overview of the evidence base underpinning the use and limitations of clofazimine as an antituberculosis drug and discuss advances in the understanding of clofazimine pharmacokinetics, toxicity, and resistance. The unusual pharmacokinetic properties of clofazimine and how these relate to its putative mechanism of action, antituberculosis activity, dosing considerations and adverse effects are highlighted. Finally, we discuss the development of novel riminophenazine analogues as antituberculosis drugs.

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PMCID: PMC9932205
PMID: 36817137

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.

3. **Surveillance of multidrug-resistant tuberculosis in Taiwan, 2008-2019.**

J Microbiol Immunol Infect. 2023 Feb;56(1):120-129. doi: 10.1016/j.jmii.2022.08.004. Epub 2022 Aug 11.

Wu MH(1), Hsiao HC(1), Chu PW(2), Chan HH(1), Lo HY(2), Jou R(3).

BACKGROUND: Drug-resistant tuberculosis (DR-TB) is a major contributor to global cases of antimicrobial resistance and remains a public health challenge. To understand the extent and trend of DR-TB under an enhanced multidrug-resistant TB (MDR-TB) management program, we conducted a population-based retrospective study of 1511 Taiwanese MDR-TB cases reported from 2008 to 2019.
METHODS: We obtained patient demographics and clinical and bacteriological information from the National TB Registry and the Infectious Disease Notification System.
RESULTS: Of the 1511 MDR-TB patients, 941 were new cases, 485 were previously treated, and 85 had an unknown history of treatment. The male to female ratio was 2.75, and the median age of the patients was 57 years (IQR: 45-72). We observed a significant decline in MDR-TB cases, with annual percentage change (APC) of -4.17%. However, new and previously treated MDR-TB cases had APCs of -1.41% and -9.18%, respectively. The rates of MDR-TB resistance to ethambutol, streptomycin and pyrazinamide were 47.2%, 42.4% and 28.9%, respectively, whereas the rates of resistance to fluoroquinolones and second-line injectable drugs (SLIDs) were 4.1-7.1%, 9.0-14.1%; and the rate of extensively drug-resistant TB was 1.9%, respectively. Furthermore, we observed a decreasing trend of resistance to SLIDs (APCs -7.0% to -8.2%) in new cases and a significant decreasing trend of resistance to moxifloxacin (-24.6%) and levofloxacin (-23.3%) in previously treated cases.
CONCLUSION: The decreasing trend of MDR-TB and resistance to second-line drugs suggested that our programmatic management of TB was effective and that the impact on TB control was profound.

DOI: 10.1016/j.jmii.2022.08.004
PMID: 35995668 [Indexed for MEDLINE]

Conflict of interest statement: Conflict of interest None.

4. **Multidrug-Resistant TB (MDR-TB) and Extensively Drug-Resistant TB (XDR-TB) Among Children: Where We Stand Now.**

Cureus. 2023 Feb 18;15(2):e35154. doi: 10.7759/cureus.35154. eCollection 2023 Feb.

Chowdhury K(1), Ahmad R(2), Sinha S(3), Dutta S(4), Haque M(5).

Drug-resistant tuberculosis (DR-TB) has continued to be a global health cataclysm. It is an arduous condition to tackle but is curable with the proper choice of drug and adherence to the drug therapy. WHO has introduced newer drugs with all-oral shorter regimens, but the COVID-19 pandemic has disrupted the achievements and raised the severity. The COVID-19 controlling mechanism is based on social distancing, using face masks, personal protective equipment, medical glove, head shoe cover, face shield, goggles, hand hygiene, and many more. Around the globe, national and international health authorities impose lockdown and movement control orders to ensure social distancing and prevent transmission of COVID-19 infection. Therefore, WHO proposed a TB control program impaired during a pandemic. Children, the most vulnerable group, suffer more from the drug-resistant form and act as the storehouse of future fatal cases. It has dire effects on physical health and hampers their mental health and academic career. Treatment of drug-resistant cases has more success stories in children than adults, but enrollment for treatment has been persistently low in this age group. Despite that, drug-resistant childhood tuberculosis has been neglected, and proper surveillance has not yet been achieved. Insufficient reporting, lack of appropriate screening tools for children, less accessibility to the treatment facility, inadequate awareness, and reduced funding for TB have worsened the situation. All these have resulted in jeopardizing our dream to terminate this deadly condition. So, it is high time to focus on this issue to achieve our Sustainable Development Goals (SDGs), the goal of ending TB by 2030, as planned by WHO. This review explores childhood TB's current position and areas to improve. This review utilized electronic-based data searched through PubMed, Google Scholar, Google Search Engine, Science Direct, and Embase.

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PMCID: PMC9938784
PMID: 36819973

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

5. **Microbiological diagnosis and mortality of tuberculosis meningitis: Systematic review and meta-analysis.**

PLoS One. 2023 Feb 16;18(2):e0279203. doi: 10.1371/journal.pone.0279203. eCollection 2023.

Seid G(1)(2), Alemu A(1)(2), Dagne B(1)(2), Gamtesa DF(1).

BACKGROUND: Tuberculosis (TB) which is caused by Mycobacterium tuberculosis poses a significant public health global treat. Tuberculosis meningitis (TBM) accounts for approximately 1% of all active TB cases. The diagnosis of Tuberculosis meningitis is notably difficult due to its rapid onset, nonspecific symptoms, and the difficulty of detecting Mycobacterium tuberculosis in cerebrospinal fluid (CSF). In 2019, 78,200 adults died of TB meningitis. This study aimed to assess the microbiological diagnosis TB meningitis using CSF and estimated the risk of death from TBM.
METHODS: Relevant electronic databases and gray literature sources were searched for studies that reported presumed TBM patients. The quality of included studies was assessed using the Joanna Briggs Institute Critical Appraisal tools designed for prevalence studies. Data were summarized using Microsoft excel ver 16. The proportion of culture confirmed TBM, prevalence of drug resistance and risk of death were calculated using the random-effect model. Stata version 16.0 was used perform the statistical analysis. Moreover, subgroup analysis was conducted.
RESULTS: After systematic searching and quality assessment, 31 studies were included in the final analysis. Ninety percent of the included studies were retrospective studies in design. The overall pooled estimates of CSF culture positive TBM was 29.72% (95% CI; 21.42-38.02). The pooled prevalence of MDR-TB among culture positive TBM cases was 5.19% (95% CI; 3.12-7.25). While, the proportion of INH mono-resistance was 9.37% (95% CI; 7.03-11.71). The pooled estimate of case fatality rate among confirmed TBM cases was 20.42% (95%CI; 14.81-26.03). Based on sub group analysis, the pooled case fatality rate among HIV positive and HIV negative TBM individuals was 53.39% (95%CI; 40.55-66.24) and 21.65% (95%CI;4.27-39.03) respectively.
CONCLUSION: Definite diagnosis of TBM still remains global treat. Microbiological confirmation of TBM is not always achievable. Early microbiological confirmation of TBM has great importance to reduce mortality. There was high rate of MDR-TB among confirmed TBM patients. All TB meningitis isolates should be cultured and drug susceptibility tested using standard techniques.

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PMCID: PMC9934382
PMID: 36795648 [Indexed for MEDLINE]

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

interests exist.

6. **Epidemiology and Drug Resistance Patterns of Mycobacterium tuberculosis in High-Burden Area in Western Siberia, Russia.**

Microorganisms. 2023 Feb 8;11(2):425. doi: 10.3390/microorganisms11020425.

Kostyukova I(1), Pasechnik O(2), Mokrousov I(3)(4).

Russia is a high-burden area for multidrug-resistant tuberculosis (MDR-TB). Here, we studied the epidemiological situation and drug resistance patterns of Mycobacterium tuberculosis in the Omsk region in Western Siberia. M. tuberculosis isolates (n = 851) were recovered from newly diagnosed TB patients in 2021. The isolates were tested by bacteriological and molecular methods, and long-term epidemiological data were analyzed. The TB incidence dec, this is not variablereased from 93.9 in 2012 to 48.1 in 2021, per 100,000 population, but the primary MDR-TB rate increased from 19.2% to 26.4%. The destructive forms of tuberculosis accounted for 37.8% of all cases, while 35.5% of patients were smear-positive. Of all isolates tested, 55.2% were culture-positive, of which 94.5% were further tested for phenotypic drug resistance and associated mutations. More than half (53.4%) of isolates were drug-resistant, 13.9% were monoresistant and 67.9% were MDR. Among MDR isolates, 40.4% were pre-XDR, and 19.2% were XDR. The spectrum of drug resistance included second-line drugs (new-generation fluoroquinolones, linezolid), which significantly increase the risk of an adverse outcome in patients. In conclusion, our results highlight the critical importance of monitoring drug resistance in circulating M. tuberculosis strains emerging due to ineffective treatment and active transmission.

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PMCID: PMC9963218
PMID: 36838390

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

7. **Whole-genome sequencing-based analyses of drug-resistant Mycobacterium tuberculosis from Taiwan.**

Sci Rep. 2023 Feb 13;13(1):2540. doi: 10.1038/s41598-023-29652-3.

Xiao YX(#)(1)(2), Liu KH(#)(1)(2), Lin WH(1)(2), Chan TH(1)(2), Jou R(3)(4).

Drug-resistant tuberculosis (DR-TB) posed challenges to global TB control.

Whole-genome sequencing (WGS) is recommended for predicting drug resistance to guide DR-TB treatment and management. Nevertheless, data are lacking in Taiwan. Phenotypic drug susceptibility testing (DST) of 12 anti-TB drugs was performed for 200 Mycobacterium tuberculosis isolates. WGS was performed using the Illumina platform. Drug resistance profiles and lineages were predicted in silico using the Total Genotyping Solution for TB (TGS-TB). Using the phenotypic DST results as a reference, WGS-based prediction demonstrated high concordance rates of isoniazid (95.0%), rifampicin (RIF) (98.0%), pyrazinamide (98.5%) and fluoroquinolones (FQs) (99.5%) and 96.0% to 99.5% for second-line injectable drugs (SLIDs); whereas, lower concordance rates of ethambutol (87.5%), streptomycin (88.0%) and ethionamide (84.0%). Furthermore, minimum inhibitory concentrations confirmed that RIF rpoB S450L, FQs gyrA D94G and SLIDs rrs a1401g conferred high resistance levels. Besides, we identified lineage-associated mutations in lineage 1 (rpoB H445Y and fabG1 c-15t) and predominant lineage 2 (rpoB S450L and rpsL K43R). The WGS-based prediction of drug resistance is highly concordant with phenotypic DST results and can provide comprehensive genetic information to guide DR-TB precision therapies in Taiwan.

DOI: 10.1038/s41598-023-29652-3
PMCID: PMC9925824
PMID: 36781938 [Indexed for MEDLINE]

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

8. **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
PMCID: PMC9910680
PMID: 36503203 [Indexed for MEDLINE]

Conflict of interest statement: Authors declare no conflict of interest.

9. **Osteoarticular tuberculosis cases in the southwest of China: A 9-year retrospective study.**

Front Med (Lausanne). 2023 Feb 7;10:1051620. doi: 10.3389/fmed.2023.1051620. eCollection 2023.

Wang DM(1), An Q(1), Yang Q(1), Liao Y(2), Jian Y(3).

BACKGROUND: Osteoarticular tuberculosis (TB) is an uncommon form of extrapulmonary TB. In this study, we analyzed the epidemiological characteristics, common sites, and drug resistance profiles of osteoarticular TB infections occurring in southwest China.
METHODS: A total of 3,254 cases of patients clinically diagnosed with osteoarticular TB infections between 2013 and 2021 were retrospectively analyzed. Patients' demographic and clinical characteristics were collected. Drug sensitivity testing was performed using the microporous plate ratio method. Chi-squared analysis was used to analyze the rates of and trends in mycobacterial isolates.
RESULTS: Of the 3,254 patients, 1,968 (60.5%) were men and boys, and 1,286 (39.5%) were women and girls; patients' ages ranged from 1 to 91 years, with an average of 42 ± 19.3 years. In terms of disease, 2,261 (69.5%) had spinal TB, mainly thoracic (815, 36%) or lumbar (1,080, 48%); joint TB was found in 874 cases (26.9%), mainly occurring in the knee (263, 30%) or hip (227, 26%); and

both spinal and joint TB were observed in 119 cases (3.7%). Drug susceptibility tests were performed on 241 isolated strains of MTB; 70 strains (29.0%) were resistant to at least one drug, and MDR-TB and XDR-TB were observed in 7.1 and 1.2% of strains, respectively.
CONCLUSIONS: In southwest China over this period, osteoarticular TB mainly affected middle-aged and young men with poor nutritional status. Patients from ethnic minority areas also accounted for a large proportion of cases. Spinal TB is prone to occur in the lumbar and thoracic vertebrae, and joint TB is prone to occur in the lower limb joints. Additionally, there has been an increasing trend in the number of TB cases over the past 9 years, and drug resistance has also increased.

DOI: 10.3389/fmed.2023.1051620
PMCID: PMC9941672
PMID: 36824612

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.

10. **New insights on tuberculosis transmission dynamics and drug susceptibility profiles among the prison population in Southern Brazil based on whole-genome sequencing.**

Rev Soc Bras Med Trop. 2023 Feb 20;56:e0181. doi: 10.1590/0037-8682-0181-2022. eCollection 2023.

Anselmo LMP(1), Gallo JF(2), Pinhata JMW(2), Peronni KC(3), Silva Junior WAD(4), Ruy PC(5), Conceição EC(6), Dippenaar A(7), Warren RM(6), Monroe AA(8), Oliveira RS(2), Bollela VR(1).

BACKGROUND: The rate of tuberculosis (TB) infection among the prison population (PP) in Brazil is 28 times higher than that in the general population, and prison environment favors the spread of TB.
OBJECTIVE: To describe TB transmission dynamics and drug resistance profiles in PP using whole-genome sequencing (WGS).
METHODS: This was a retrospective study of Mycobacterium tuberculosis cultivated from people incarcerated in 55 prisons between 2016 and 2019; only one isolate per prisoner was included. Information about movement from one prison to another was tracked. Clinical information was collected, and WGS was performed on isolates obtained at the time of TB diagnosis.

RESULTS: Among 134 prisoners included in the study, we detected 16 clusters with a total of 58 (43%) cases of M. tuberculosis. Clusters ranged from two to seven isolates with five or fewer single nucleotide polymorphism (SNP) differences, suggesting a recent transmission. Six (4.4%) isolates were resistant to at least one anti-TB drug. Two of these clustered together and showed resistance to rifampicin, isoniazid, and fluoroquinolones, with 100% concordance between WGS and phenotypic drug-susceptibility testing. Prisoners with clustered isolates had a high amount of movement between prisons (two to eight moves) during the study period.
CONCLUSIONS: WGS demonstrated the recent transmission of TB within prisons in Brazil. The high movement among prisoners seems to be related to the transmission of the same M. tuberculosis strain within the prison system. Screening for TB before and after the movement of prisoners using rapid molecular tests could play a role in reducing transmission.

DOI: 10.1590/0037-8682-0181-2022
PMCID: PMC9957134
PMID: 36820651 [Indexed for MEDLINE]

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

11. **Nationwide Treatment Outcomes of Patients With Multidrug/Rifampin-Resistant Tuberculosis in Korea, 2011-2017: A Retrospective Cohort Study (Korean TB-POST).**

J Korean Med Sci. 2023 Feb 6;38(5):e33. doi: 10.3346/jkms.2023.38.e33.

Choi H(1), Mok J(2), Kang YA(3), Jeong D(4), Kang HY(5), Kim HJ(6), Kim HS(7), Jeon D(8).

BACKGROUND: The treatment outcomes of patients with multidrug/rifampin-resistant (MDR/RR) tuberculosis (TB) are important indicators that reflect the current status of TB management and identify the key challenges encountered by TB control programs in a country.
METHODS: We retrospectively evaluated the treatment outcomes as well as predictors of unfavorable outcomes in patients with MDR/RR-TB notified from 2011 to 2017, using an integrated TB database.
RESULTS: A total of 7,226 patients with MDR/RR-TB were included. The treatment success rate had significantly increased from 63.9% in 2011 to 75.1% in 2017 ($P < 0.001$). Among unfavorable outcomes, the proportion of patients who failed, were lost to follow up, and were not evaluated had gradually decreased ($P < 0.001$). In contrast, TB-related death rate was not significantly changed ($P = 0.513$), while the non-TB related death rate had increased from 3.2% in 2011 to

11.1% in 2017 (P < 0.001). Older age, male sex, immigrants, low household income, previous history of TB treatment, and comorbidities were independent predictors of unfavorable outcomes. Of the 5,308 patients who were successfully treated, recurrence occurred in 241 patients (4.5%) at a median 18.4 months (interquartile range, 9.2-32.4) after completion treatment.
CONCLUSION: The treatment outcomes of patients with MDR/RR-TB has gradually improved but increasing deaths during treatment is an emerging challenge for MDR-TB control in Korea. Targeted and comprehensive care is needed for vulnerable patients such as the elderly, patients with comorbidities, and those with low household incomes.

DOI: 10.3346/jkms.2023.38.e33
PMCID: PMC9902661
PMID: 36747362 [Indexed for MEDLINE]

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

12. **Cross-municipality migration and spread of tuberculosis in South Africa.**

Sci Rep. 2023 Feb 15;13(1):2674. doi: 10.1038/s41598-023-29804-5.

Fofana AM(1)(2), Moultrie H(3), Scott L(4), Jacobson KR(5), Shapiro AN(6), Dor G(4), Crankshaw B(3), Silva PD(7), Jenkins HE(6), Bor J(8)(6), Stevens WS(4)(7).

Human migration facilitates the spread of infectious disease. However, little is known about the contribution of migration to the spread of tuberculosis in South Africa. We analyzed longitudinal data on all tuberculosis test results recorded by South Africa's National Health Laboratory Service (NHLS), January 2011-July 2017, alongside municipality-level migration flows estimated from the 2016 South African Community Survey. We first assessed migration patterns in people with laboratory-diagnosed tuberculosis and analyzed demographic predictors. We then quantified the impact of cross-municipality migration on tuberculosis incidence in municipality-level regression models. The NHLS database included 921,888 patients with multiple clinic visits with TB tests. Of these, 147,513 (16%) had tests in different municipalities. The median (IQR) distance travelled was 304 (163 to 536) km. Migration was most common at ages 20-39 years and rates were similar for men and women. In municipality-level regression models, each 1% increase in migration-adjusted tuberculosis prevalence was associated with a 0.47% (95% CI: 0.03% to 0.90%) increase in the incidence of drug-susceptible tuberculosis two years later, even after controlling for baseline prevalence.

Similar results were found for rifampicin-resistant tuberculosis. Accounting for migration improved our ability to predict future incidence of tuberculosis.

DOI: 10.1038/s41598-023-29804-5
PMCID: PMC9930008
PMID: 36792792 [Indexed for MEDLINE]

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

13. **A systematic review of risk factors for mortality among tuberculosis patients in South Africa.**

Syst Rev. 2023 Feb 23;12(1):23. doi: 10.1186/s13643-023-02175-8.

Nicholson TJ(1), Hoddinott G(1), Seddon JA(1)(2), Claassens MM(1)(3), van der Zalm MM(1), Lopez E(1)(4), Bock P(1), Caldwell J(5), Da Costa D(6), de Vaal C(7), Dunbar R(1), Du Preez K(1), Hesseling AC(1), Joseph K(5), Kriel E(8), Loveday M(9)(10), Marx FM(1)(11), Meehan SA(1), Purchase S(1), Naidoo K(10), Naidoo L(5), Solomon-Da Costa F(5), Sloot R(1), Osman M(12)(13).

BACKGROUND: Tuberculosis (TB)-associated mortality in South Africa remains high. This review aimed to systematically assess risk factors associated with death during TB treatment in South African patients.
METHODS: We conducted a systematic review of TB research articles published between 2010 and 2018. We searched BioMed Central (BMC), PubMed®, EBSCOhost, Cochrane, and SCOPUS for publications between January 2010 and December 2018. Searches were conducted between August 2019 and October 2019. We included randomised control trials (RCTs), case control, cross sectional, retrospective, and prospective cohort studies where TB mortality was a primary endpoint and effect measure estimates were provided for risk factors for TB mortality during TB treatment. Due to heterogeneity in effect measures and risk factors evaluated, a formal meta-analysis of risk factors for TB mortality was not appropriate. A random effects meta-analysis was used to estimate case fatality ratios (CFRs) for all studies and for specific subgroups so that these could be compared. Quality assessments were performed using the Newcastle-Ottawa scale or the Cochrane Risk of Bias Tool.
RESULTS: We identified 1995 titles for screening, 24 publications met our inclusion criteria (one cross-sectional study, 2 RCTs, and 21 cohort studies). Twenty-two studies reported on adults (n = 12561) and two were restricted to children < 15 years of age (n = 696). The CFR estimated for all studies was 26.4% (CI 18.1-34.7, n = 13257); 37.5% (CI 24.8-50.3, n = 5149) for

drug-resistant (DR) TB; 12.5% (CI 1.1-23.9, n = 1935) for drug-susceptible (DS) TB; 15.6% (CI 8.1-23.2, n = 6173) for studies in which drug susceptibility was mixed or not specified; 21.3% (CI 15.3-27.3, n = 7375) for people living with HIV/AIDS (PLHIV); 19.2% (CI 7.7-30.7, n = 1691) in HIV-negative TB patients; and 6.8% (CI 4.9-8.7, n = 696) in paediatric studies. The main risk factors associated with TB mortality were HIV infection, prior TB treatment, DR-TB, and lower body weight at TB diagnosis.
CONCLUSIONS: In South Africa, overall mortality during TB treatment remains high, people with DR-TB have an elevated risk of mortality during TB treatment and interventions to mitigate high mortality are needed. In addition, better prospective data on TB mortality are needed, especially amongst vulnerable sub-populations including young children, adolescents, pregnant women, and people with co-morbidities other than HIV. Limitations included a lack of prospective studies and RCTs and a high degree of heterogeneity in risk factors and comparator variables.
SYSTEMATIC REVIEW REGISTRATION: The systematic review protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the registration number CRD42018108622. This study was funded by the Bill and Melinda Gates Foundation (Investment ID OPP1173131) via the South African TB Think Tank.

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PMCID: PMC9946877
PMID: 36814335 [Indexed for MEDLINE]

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

14. **Designing molecular diagnostics for current tuberculosis drug regimens.**

Emerg Microbes Infect. 2023 Feb 8:2178243. doi: 10.1080/22221751.2023.2178243. Online ahead of print.

Georghiou SB(1), de Vos M(1), Velen K(1), Miotto P(2), Colman RE(1)(3), Cirillo DM(2), Ismail N(4), Rodwell TC(1)(3), Suresh A(1), Ruhwald M(1).

Diagnostic development must occur in parallel with drug development to ensure the longevity of new treatment compounds. Despite an increasing number of novel and repurposed anti-tuberculosis compounds and regimens, there remains a large number of drugs for which no rapid and accurate molecular diagnostic option exists. The lack of rapid drug susceptibility testing for linezolid,

bedaquiline, clofazimine, the nitroimidazoles (i.e pretomanid and delamanid) and pyrazinamide at any level of the healthcare system compromises the effectiveness of current tuberculosis and drug-resistant tuberculosis treatment regimens. In the context of current WHO tuberculosis treatment guidelines as well as promising new regimens, we identify the key diagnostic gaps for initial and follow-on tests to diagnose emerging drug resistance and aid in regimen selection. Additionally, we comment on potential gene targets for inclusion in rapid molecular drug susceptibility assays and sequencing assays for novel and repurposed drug compounds currently prioritized in current regimens, and evaluate the feasibility of mutation detection given the design of existing technologies. Based on current knowledge, we also propose design priorities for next generation molecular assays to support triage of tuberculosis patients to appropriate and effective treatment regimens. We encourage assay developers to prioritize development of these key molecular assays and support the continued evolution, uptake, and utility of sequencing to build knowledge of tuberculosis resistance mechanisms and further inform rapid treatment decisions in order to curb resistance to critical drugs in current regimens and achieve End TB targets.Trial registration: ClinicalTrials.gov identifier: NCT05117788..

DOI: 10.1080/22221751.2023.2178243
PMID: 36752055

15. **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.

16. **Variation in missed doses and reasons for discontinuation of anti-tuberculosis drugs during hospital treatment for drug-resistant tuberculosis in South Africa.**

PLoS One. 2023 Feb 13;18(2):e0281097. doi: 10.1371/journal.pone.0281097. eCollection 2023.

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

BACKGROUND: Updated World Health Organization (WHO) treatment guidelines prioritize all-oral drug-resistant tuberculosis (DR-TB) regimens. Several poorly tolerated drugs, such as amikacin and para-aminosalicylic acid (PAS), remain treatment options for DR-TB in WHO-recommended longer regimens as Group C drugs. Incomplete treatment with anti-TB drugs increases the risk of treatment failure, relapse, and death. We determined whether missed doses of individual anti-TB drugs, and reasons for their discontinuation, varied in closely monitored hospital settings prior to the 2020 WHO DR-TB treatment guideline updates.
METHODS: We collected retrospective data on adult patients with microbiologically confirmed DR-TB between 2008 and 2015 who were selected for a study of acquired drug resistance in the Western Cape Province of South Africa. Medical records through mid-2017 were reviewed. Patients received directly observed treatment during hospitalization at specialized DR-TB hospitals. Incomplete treatment with individual anti-TB drugs, defined as the failure to take medication as prescribed, regardless of reason, was determined by comparing percent missed doses, stratified by HIV status and DR-TB regimen. We applied a generalized mixed effects model.

RESULTS: Among 242 patients, 131 (54%) were male, 97 (40%) were living with HIV, 175 (72%) received second-line treatment prior to first hospitalization, and 191 (79%) died during the study period. At initial hospitalization, 134 (55%) patients had Mycobacterium tuberculosis with resistance to rifampicin and isoniazid (multidrug-resistant TB [MDR-TB]) without resistance to ofloxacin or amikacin, and 102 (42%) had resistance to ofloxacin and/or amikacin. Most patients (129 [53%]) had multiple hospitalizations and DST changes occurred in 146 (60%) by the end of their last hospital discharge. Incomplete treatment was significantly higher for amikacin (18%), capreomycin (18%), PAS (17%) and kanamycin (16%) than other DR-TB drugs (P<0.001), including ethionamide (8%), moxifloxacin (7%), terizidone (7%), ethambutol (7%), and pyrazinamide (6%). Among the most frequently prescribed drugs, second-line injectables had the highest rates of discontinuation for adverse events (range 0.56-1.02 events per year follow-up), while amikacin, PAS and ethionamide had the highest rates of discontinuation for patient refusal (range 0.51-0.68 events per year follow-up). Missed doses did not differ according to HIV status or anti-TB drug combinations.
CONCLUSION: We found that incomplete treatment for second-line injectables and PAS during hospitalization was higher than for other anti-TB drugs. To maximize treatment success, interventions to improve person-centered care and mitigate adverse events may be necessary in cases when PAS or amikacin (2020 WHO recommended Group C drugs) are needed.

DOI: 10.1371/journal.pone.0281097
PMCID: PMC9925007
PMID: 36780443 [Indexed for MEDLINE]

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

17. **Patients' perceived quality of care and their satisfaction with care given for MDR-TB at referral hospitals in Ethiopia.**

PLoS One. 2023 Feb 2;18(2):e0270439. doi: 10.1371/journal.pone.0270439. eCollection 2023.

Wakjira MK(1), Sandy PT(2), Mavhandu-Mudzusi AH(3).

BACKGROUND: There is presently dearth of evidence in Ethiopia on patients' perception on quality of care given for multi-drug resistant tuberculosis (MDR-TB) and their satisfaction with the care and services they receive for the disease. Moreover, there is no evidence on the experiences and practices of caregivers for MDR-TB regarding the functionality of the programmatic management of MDR-TB at referral hospitals in Ethiopia. Thus, this study was conducted to address these gaps. Evidence in these areas would help to institute interventions that could enhance patient satisfaction and their adherence to the treatment given for MDR-TB.
DESIGN AND METHODS: This study employed an inductive phenomenological approach to investigate patients' perception of the quality of care given for MDR-TB, level of their satisfaction with the care they received for MDR-TB and the experiences and practices of caregivers for MDR-TB on the functionality of the programmatic management of MDR-TB at referral hospitals in Ethiopia. The data were analysed manually, and that helped to get more control over the data.
RESULTS: The majority of the patients were satisfied with the compassionate communication and clinical care they received at hospitals. However, as no doctor was dedicated exclusively for the MDR-TB centre of the hospitals, patients could not get timely medical attention during emergent medical conditions. Patients were dissatisfied with the poor communication and uncaring practice of caregivers found at treatment follow-up centres (TFCs). Patients perceived that socio-economic difficulties are both the cause of MDR-TB and it has also challenged their ability to cope-up with the disease and its treatment. Patients were dissatisfied with the poor quality and inadequate quantity of the socio-economic support they got from the programme. Despite the high MDR-TB and HIV/AIDS co-infection, services for both diseases were not available under one roof.
CONCLUSIONS: Socio-economic challenges, inadequate socio-economic support, absence of integrated care for MDR-TB and HIV/AIDS, and the uncaring practice of caregivers at treatment follow-up centres are found to negatively affect patients' perceived quality of care and their satisfaction with the care given for MDR-TB. Addressing these challenges is recommended to assist patients' coping ability with MDR-TB and its treatment.

DOI: 10.1371/journal.pone.0270439
PMCID: PMC9894439
PMID: 36730222 [Indexed for MEDLINE]

Conflict of interest statement: During the time the research was conducted one

of the authors was employed to Abt Associates Inc. operating in Ethiopia. The authors hereby confirm that this does not alter our adherence to PLOS ONE policies on sharing data and materials.

18. **Catastrophic Costs among Tuberculosis-Affected Households in Egypt: Magnitude, Cost Drivers, and Coping Strategies.**

Int J Environ Res Public Health. 2023 Feb 1;20(3):2640. doi: 10.3390/ijerph20032640.

Ghazy RM(1), Sallam M(2)(3), Ashmawy R(4), Elzorkany AM(5), Reyad OA(6), Hamdy NA(7), Khedr H(8), Mosallam RA(9).

Despite national programs covering the cost of treatment for tuberculosis (TB) in many countries, TB patients still face substantial costs. The end TB strategy, set by the World Health Organization (WHO), calls for "zero" TB households to be affected by catastrophic payments by 2025. This study aimed to measure the catastrophic healthcare payments among TB patients in Egypt, to determine its cost drivers and determinants and to describe the coping strategies. The study utilized an Arabic-validated version of the TB cost tool developed by the WHO for estimating catastrophic healthcare expenditure using the cluster-based sample survey with stratification in seven administrative regions in Alexandria. TB payments were considered catastrophic if the total cost exceeded 20% of the household's annual income. A total of 276 patients were interviewed: 76.4% were males, 50.0% were in the age group 18-35, and 8.3% had multidrug-resistant TB. Using the human capital approach, 17.0% of households encountered catastrophic costs compared to 59.1% when using the output approach. The cost calculation was carried out using the Egyptian pound converted to the United States dollars based on 2021 currency values. Total TB cost was United States dollars (USD) 280.28 ± 29.9 with a total direct cost of USD 103 ± 10.9 and a total indirect cost of USD 194.15 ± 25.5. The direct medical cost was the main cost driver in the pre-diagnosis period (USD 150.23 ± 26.89 pre diagnosis compared to USD 77.25 ± 9.91 post diagnosis, $p = 0.013$). The indirect costs (costs due to lost productivity) were the main cost driver in the post-diagnosis period (USD 4.68 ± 1.18 pre diagnosis compared to USD 192.84 ± 25.32 post diagnosis, $p < 0.001$). The households drew on multiple financial strategies to cope with TB costs where 66.7% borrowed and 25.4% sold household property. About two-thirds lost their jobs and another two-thirds lowered their food intake. Being female, delay in diagnosis and being in the intensive phase were significant predictors of catastrophic payment. Catastrophic costs were high among TB households in Alexandria and showed wide variation according to the method used for indirect cost estimation. The main cost driver before diagnosis was the direct medical costs, while it was the indirect costs, post diagnosis.

DOI: 10.3390/ijerph20032640
PMCID: PMC9915462
PMID: 36768005 [Indexed for MEDLINE]

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

19. **A case report about a child with drug-resistant tuberculous meningitis.**

BMC Infect Dis. 2023 Feb 7;23(1):83. doi: 10.1186/s12879-023-07990-x.

Tong J(1), Gao M(2), Chen Y(3), Wang J(3).

BACKGROUND: Hematogenous disseminated tuberculosis predisposes to concurrent tuberculous meningitis (TBM), the most devastating and disabling form of tuberculosis. However, children often have atypical clinical symptoms, difficulty in specimen collection, low specimen content, and an increasing incidence of drug-resistant tuberculosis. Thus, the accurate diagnosis and timely treatment of childhood tuberculosis face monumental challenges.
CASE PRESENTATION: The 14-year-old female presented to the hospital with intermittent fever, headache, and blurred vision. Her cerebrospinal fluid (CSF) showed a lymphocytic pleocytosis, an elevated protein level, and a decreased chloride level. And her CSF tested positive for TB-RNA. Xpert MTB/RIF detected Mycobacterium tuberculosis in her CSF, but the rifampin resistance test was unknown. Subsequently, her CSF culture was positive for Mycobacterium tuberculosis. The drug sensitivity test (DST) revealed resistance to isoniazid, rifampin, and fluoroquinolones. A computed tomography (CT) of the chest showed diffuse miliary nodules in both lungs. Intracranial enhanced magnetic resonance imaging (MRI) showed "multiple intensified images of the brain parenchyma, cisterns, and part of the meninges." The final diagnosis is miliary pulmonary tuberculosis and pre-extensive drug-resistant TBM. After 19 months of an oral, individualized antituberculosis treatment, she recovered with no significant neurological sequelae.
CONCLUSION: For patients with miliary pulmonary tuberculosis, especially children, even if there are no typical clinical symptoms, it is necessary to know whether there is TBM and other conditions. Always look for the relevant aetiological basis to clarify whether it is drug-resistant tuberculosis. Only a rapid and accurate diagnosis and timely and effective treatment can improve the prognosis and reduce mortality and disability rates.

DOI: 10.1186/s12879-023-07990-x

PMCID: PMC9906903
PMID: 36750780 [Indexed for MEDLINE]

Conflict of interest statement: None.

20. **Non-actionable Results, Accuracy, and Effect of First- and Second-line Line Probe Assays for Diagnosing Drug-Resistant Tuberculosis, Including on Smear-Negative Specimens, in a High-Volume Laboratory.**

Clin Infect Dis. 2023 Feb 8;76(3):e920-e929. doi: 10.1093/cid/ciac556.

Pillay S(1)(2), de Vos M(1), Derendinger B(1), Streicher EM(1), Dolby T(2), Scott LA(1), Steinhobel AD(1), Warren RM(1), Theron G(1).

BACKGROUND: Rapid tuberculosis (TB) drug susceptibility testing (DST) is crucial. Genotype MTBDRsl is a widely deployed World Health Organization (WHO)-endorsed assay. Programmatic performance data, including non-actionable results from smear-negative sputum, are scarce.
METHODS: Sputa from Xpert MTB/RIF individuals (n = 951) were routinely-tested using Genotype MTBDRplus and MTBDRsl (both version 2). Phenotypic DST was the second-line drug reference standard. Discrepant results underwent Sanger sequencing.
FINDINGS: 89% (849 of 951) of individuals were culture-positive (56%, 476 of 849 smear-negative). MTBDRplus had at least 1 nonactionable result (control and/or TB-detection bands absent or invalid, precluding resistance reporting) in 19% (92 of 476) of smear-negatives; for MTBDRsl, 40% (171 of 427) were nonactionable (28%, 120 of 427 false-negative TB; 17%, 51 of 427 indeterminate). In smear-negatives, MTBDRsl sensitivity for fluoroquinolones was 84% (95% confidence interval, 67%-93), 81% (54%-95%) for second-line injectable drugs, and 57% (28%-82%) for both. Specificities were 93% (89%-98%), 88% (81%-93%), and 97% (91%-99%), respectively. Twenty-three percent (172 of 746) of Xpert rifampicin-resistant specimens were MTBDRplus isoniazid-susceptible. Days-to-second-line-susceptibility reporting with the programmatic advent of MTBDRsl improved (6 [5-7] vs 37 [35-46]; P < .001).
CONCLUSIONS: MTBDRsl did not generate a result in 4 of 10 smear-negatives, resulting in substantial missed resistance. However, if MTBDRsl generates an actionable result, that is accurate in ruling-in resistance. Isoniazid DST remains crucial. This study provides real-world, direct, second-line susceptibility testing performance data on non-actionable results (that, if unaccounted for, cause an overestimation of test utility), accuracy, and care cascade impact.

DOI: 10.1093/cid/ciac556
PMCID: PMC7614164
PMID: 35788278 [Indexed for MEDLINE]

Conflict of interest statement: Potential conflicts of interest. The authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

21. **Trials underestimate the impact of preventive treatment for household contacts exposed to multidrug-resistant tuberculosis: a simulation study.**

medRxiv. 2023 Feb 8:2023.02.06.23285528. doi: 10.1101/2023.02.06.23285528. Preprint.

Kasaie P, Pennington J, Gupta A, Dowdy DW, Kendall EA.

BACKGROUND: Several clinical trials of tuberculosis preventive treatment (TPT) for household contacts of patients with multidrug-resistant tuberculosis (MDR-TB) are nearing completion. The potential benefits of TPT for MDR-TB contacts extend beyond the outcomes that clinical trials can measure.
METHODS: We developed an agent-based, household-structured TB and MDR-TB transmission model, calibrated to an illustrative setting in India, the country accounting for 26% of global MDR-TB burden. We simulated household contact investigation for contacts of patients with MDR-TB, comparing an MDR-TPT regimen against alternatives of isoniazid preventive treatment, household contact investigation without TPT, or no household contact intervention. We simulated outcomes of a clinical trial and estimated the patient-level and population-level effects over a longer time horizon.
FINDINGS: During two years of follow-up per recipient, a simulated 6-month MDR-TPT regimen with 70% efficacy against both DS- and MDR-TB infection could prevent 72% [Interquartile range (IQR): 45 - 100%] of incident MDR-TB among TPT recipients (number needed to treat (NNT) 73 [44 - 176] to prevent one MDR-TB case), compared to household contact investigation without TPT. This NNT decreased to 54 [30 - 183] when median follow-up was increased from two to 16 years, to 27 [11 - Inf] when downstream transmission effects were also considered, and to 12 [8 - 22] when these effects were compared to a scenario of no household contact intervention.
INTERPRETATION: If forthcoming trial results demonstrate efficacy, the long-term population impact of MDR-TPT implementation could be much greater than suggested by trial outcomes alone.

FUNDING: NIH K01AI138853 and K08AI127908; Johns Hopkins Catalyst Award.

DOI: 10.1101/2023.02.06.23285528
PMCID: PMC9934809
PMID: 36798407

22. **The development of the national tuberculosis research priority in Indonesia: A comprehensive mixed-method approach.**

PLoS One. 2023 Feb 9;18(2):e0281591. doi: 10.1371/journal.pone.0281591. eCollection 2023.

Lestari T(1), Fuady A(2)(3)(4), Yani FF(5), Putra IWGAE(6), Pradipta IS(7), Chaidir L(8), Handayani D(9), Fitriangga A(10), Loprang MR(11), Pambudi I(12), Ruslami R(13), Probandari A(14).

Ranked second in global tuberculosis (TB) incidence, Indonesia has developed a National Strategy for TB Prevention and Control 2020-2024 to accelerate the TB elimination program. Research and innovation are key pillars to support the program and need to be prioritised. This study aimed to develop updated national TB research priorities in Indonesia. This study was a mixed-methods study consisting of an open survey, a published literature survey, and Delphi survey. The open survey invited all related TB stakeholders to answer (a) the main barriers of the TB program and (b) the need for studies to support TB elimination. The published literature survey retrieved scientific articles published in national and international journals between 2015 and 2020 to identify gaps between published research and the current national strategy for TB control. The online survey and literature survey informed a panel of TB experts in a two-phase Delphi Survey to select the top 10 priority research topics. We identified 322 articles and analysed 1143 open survey responses. Through two-phases Delphi surveys, top ten research categories were listed: early TB detection; diagnosis and treatment of DR-TB; contact investigation; case detection and treatment of child TB; TB preventive therapy; government policy; laboratory for drug-sensitive- and drug-resistant-TB diagnosis; treatment adherence; diagnostic tool development; and community empowerment. This study also found the gap between stakeholders' interests and the importance of translating research into policy and practice. TB research priorities have been identified through the involvement of various stakeholders. The combination of an online survey, a published literature survey, and a Delphi survey was a rigorous methodology and was fit to build a systematic consensus about the priority of TB research.

DOI: 10.1371/journal.pone.0281591
PMCID: PMC9910756
PMID: 36758064 [Indexed for MEDLINE]

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

23. **Limited effect of reducing pulmonary tuberculosis incidence amid mandatory facial masking for COVID-19.**

Respir Res. 2023 Feb 17;24(1):54. doi: 10.1186/s12931-023-02365-x.

Lin EC(1), Tu HP(2), Hong CH(3)(4).

Although the incidence and mortality rates associated with tuberculosis (TB) have been decreasing in many countries, TB remains a major public health concern. Obligatory facial masking and reduced health-care capacity because of COVID-19 may substantially influence TB transmission and care. The Global Tuberculosis Report 2021 published by the World Health Organization indicated a TB rebound at the end of 2020, which coincided with the COVID-19 pandemic. We explored this rebound phenomenon in Taiwan by investigating whether TB incidence and mortality are affected by COVID-19 because of their common route of transmission. In addition, we investigated whether the incidence of TB varies across regions with different incidences of COVID-19. Data (2010-2021) regarding annual new cases of TB and multidrug-resistant TB were collected from the Taiwan Centers for Disease Control. TB incidence and mortality were assessed in Taiwan's seven administrative regions. Over the last decade, TB incidence decreased continually, even during 2020 and 2021, the years coinciding with the COVID-19 pandemic. Notably, TB incidence remained high in regions with low COVID-19 incidence. However, the overall decreasing trends of TB incidence and mortality remained unchanged during the pandemic. Facial masking and social distancing may prevent COVID-19 transmission but exhibit limited efficacy in reducing TB transmission. Thus, during health-related policymaking, policymakers must consider TB rebound, even in the post-COVID-19 era.

DOI: 10.1186/s12931-023-02365-x
PMCID: PMC9936458

PMID: 36803383 [Indexed for MEDLINE]

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

24. **Pharmacokinetic-Pharmacodynamic Determinants of Clinical Outcomes for Rifampin-Resistant Tuberculosis: A Multisite Prospective Cohort Study.**

Clin Infect Dis. 2023 Feb 8;76(3):497-505. doi: 10.1093/cid/ciac511.

Heysell SK(1), Mpagama SG(2)(3), Ogarkov OB(4), Conaway M(5), Ahmed S(6), Zhdanova S(4), Pholwat S(1), Alshaer MH(7), Chongolo AM(2), Mujaga B(3), Sariko M(3), Saba S(6), Rahman SMM(6), Uddin MKM(6), Suzdalnitsky A(8), Moiseeva E(8), Zorkaltseva E(9), Koshcheyev M(8), Vitko S(1), Mmbaga BT(3), Kibiki GS(3), Pasipanodya JG(10), Peloquin CA(7), Banu S(6), Houpt ER(1).

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(10)Quantitative Preclinical & Clinical Sciences Department, Praedicare Inc, Dallas, Texas, USA.

BACKGROUND: Rifampin-resistant and/or multidrug-resistant tuberculosis (RR/MDR-TB) treatment requires multiple drugs, and outcomes remain suboptimal. Some drugs are associated with improved outcome. It is unknown whether particular pharmacokinetic-pharmacodynamic relationships predict outcome.
METHODS: Adults with pulmonary RR/MDR-TB in Tanzania, Bangladesh, and the Russian Federation receiving local regimens were enrolled from June 2016 to July

2018. Serum was collected after 2, 4, and 8 weeks for each drug's area under the concentration-time curve over 24 hours (AUC0-24). Quantitative susceptibility of the M. tuberculosis isolate was measured by minimum inhibitory concentrations (MICs). Individual drug AUC0-24/MIC targets were assessed by adjusted odds ratios (ORs) for favorable treatment outcome, and hazard ratios (HRs) for time to sputum culture conversion. K-means clustering algorithm separated the cohort of the most common multidrug regimen into 4 clusters by AUC0-24/MIC exposures.
RESULTS: Among 290 patients, 62 (21%) experienced treatment failure, including 30 deaths. Moxifloxacin AUC0-24/MIC target of 58 was associated with favorable treatment outcome (OR, 3.75; 95% confidence interval, 1.21-11.56; P = .022); levofloxacin AUC0-24/MIC of 118.3, clofazimine AUC0-24/MIC of 50.5, and pyrazinamide AUC0-24 of 379 mg × h/L were associated with faster culture conversion (HR >1.0, P < .05). Other individual drug exposures were not predictive. Clustering by AUC0-24/MIC revealed that those with the lowest multidrug exposures had the slowest culture conversion.
CONCLUSIONS: Amidst multidrug regimens for RR/MDR-TB, serum pharmacokinetics and M. tuberculosis MICs were variable, yet defined parameters to certain drugs-fluoroquinolones, pyrazinamide, clofazimine-were predictive and should be optimized to improve clinical outcome.
CLINICAL TRIALS REGISTRATION: NCT03559582.

DOI: 10.1093/cid/ciac511
PMCID: PMC9907514
PMID: 35731948 [Indexed for MEDLINE]

Conflict of interest statement: Potential conflicts of interest. S. K. H., C. A. P., and E. R. H. report grants or contracts from the NIH outside of the submitted work. All remaining authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

26. **Design, Synthesis and Antimicrobial Evaluation of New N-(1-Hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-6-yl)(hetero)aryl-2-carboxamides as Potential Inhibitors of Mycobacterial Leucyl-tRNA Synthetase.**

Int J Mol Sci. 2023 Feb 2;24(3):2951. doi: 10.3390/ijms24032951.

Šlechta P(1), Needle AA(1), Jand'ourek O(2), Paterová P(3), Konečná K(2), Bárta P(4), Kuneš J(5), Kubíček V(4), Doležal M(1), Kučerová-Chlupáčová M(1).

Tuberculosis remains a serious killer among infectious diseases due to its incidence, mortality, and occurrence of resistant mycobacterial strains. The challenge to discover new antimycobacterial agents forced us to prepare a series of N-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-6-yl)(hetero)aryl-2-carboxamides 1-19 via the acylation of 6-aminobenzo[c][1,2]oxaborol-1(3H)-ol with various activated (hetero)arylcarboxylic acids. These novel compounds have been tested in vitro against a panel of clinically important fungi and bacteria, including mycobacteria. Some of the compounds inhibited the growth of mycobacteria in the range of micromolar concentrations and retained this activity also against multidrug-resistant clinical isolates. Half the maximal inhibitory concentrations against the HepG2 cell line indicated an acceptable toxicological profile. No growth inhibition of other bacteria and fungi demonstrated selectivity of the compounds against mycobacteria. The structure-activity relationships have been derived and supported with a molecular docking study, which confirmed a selectivity toward the potential target leucyl-tRNA synthetase without an impact on the human enzyme. The presented compounds can become important materials in antimycobacterial research.

DOI: 10.3390/ijms24032951
PMCID: PMC9917560
PMID: 36769275 [Indexed for MEDLINE]

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

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

J Pharm Biomed Anal. 2023 Feb 3;227:115281. doi: 10.1016/j.jpba.2023.115281. Online ahead of print.

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

The penetration of the antituberculosis drug delamanid into the central nervous system is not established. The distribution of delamanid and its major metabolite, DM-6705, into the cerebrospinal fluid requires investigation. A liquid chromatography-tandem mass spectrometry method for the quantification of delamanid and DM-6705 in human cerebrospinal fluid was developed and validated. The calibration range for both analytes was 0.300 - 30.0 ng/mL. The deuterium-labelled analogue of delamanid (delamanid-d4) and OPC-14714 were used

as internal standards for delamanid and DM-6705, respectively. Samples were processed by protein precipitation followed by on-line solid-phase extraction and high-performance liquid chromatography on an Agilent 1260 HPLC system. A Phenomenex Gemini-NX C18 (5.0 µm, 50 mm × 2.0 mm) analytical column was used for on-line solid-phase extraction, and a Waters Xterra MS C18 (5.0 µm, 100 mm × 2.1 mm) analytical column for chromatographic separation using gradient elution, at a flow rate of 300 µL/min. The total run time was 7.5 min. Analytes were detected by multiple reaction monitoring on an AB Sciex 5500 triple quadrupole mass spectrometer at unit mass resolution, with electrospray ionization in the positive mode. Accuracy and precision were assessed over three independent validation batches. Extraction recoveries were more than 98% and were consistent across the analytical range. Both analytes in CSF exhibited non-specific adsorption to polypropylene tubes. The method was used to analyse cerebrospinal fluid samples from patients with pulmonary tuberculosis in an exploratory pharmacokinetic study.

DOI: 10.1016/j.jpba.2023.115281
PMID: 36739721

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.

28. **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.

29. **Grave impact of undetected rpoB I572F mutation on clinical course of multidrug-resistant tuberculosis: a case report.**

Hong Kong Med J. 2023 Feb;29(1):70-72. doi: 10.12809/hkmj219735.

Chan ACK(1), Chan MCH(2), Yip PCW(2), Yam WC(3), Chau CH(4), Lam RFM(4), Tai LB(1), Leung CC(5).

DOI: 10.12809/hkmj219735
PMID: 36810242 [Indexed for MEDLINE]

Conflict of interest statement: The authors have disclosed no conflicts of interest.

Other Literature

30. **Long-term treatment outcomes in multidrug-resistant tuberculosis.**

Clin Microbiol Infect. 2023 Feb 24:S1198-743X(23)00083-6. doi: 10.1016/j.cmi.2023.02.013. Online ahead of print.

Maier C(1), Chesov D(2), Schaub D(1), Kalsdorf B(1), Andres S(3), Friesen I(3), Reimann M(1), Lange C(4).

OBJECTIVES: We describe long-term treatment outcomes in patients with multidrug-resistant/rifampicin-resistant (MDR/RR)-tuberculosis (TB) and validate established MDR/RR-TB treatment outcome definitions.
METHODS: Among patients with MDR/RR-TB admitted to a German MDR/RR-TB referral center from 01.09.2002-29.02.2020, we compared long-term treatment outcomes derived from individual patient follow-up with treatment outcomes defined by WHO-2013, WHO-2021 and TBnet-2016.
RESULTS: In total 163 patients (mean age 35 ± standard deviation 13 years, 14/163 [8.6%] living with HIV, 109/163 [66.9%] male, 149/163 [91.4%] migrating to Germany within five years) initiated treatment for culture confirmed MDR/RR-TB. Additional drug resistance to a fluoroquinolone or a second-line injectable agent was present in 15/163 (9.2%) of Mycobacterium tuberculosis strains; resistance against both drug classes was present in 29/163 (17.8%) of strains. Median duration of MDR/RR-TB treatment was 20 months (interquartile range [IQR] 19.3-21.6) with a medium of 5 active drugs included. Median

follow-up time was 4 years (47.7 months; IQR 21.7-65.8 months). Cure was achieved in 25/163 (15.3%), 82/163 (50.3%) and 95/163 (58.3%) of patients according to WHO-2013, WHO-2021, and TBnet-2016 outcome definitions, respectively. The lost to follow-up rate was 17/163 (10.4%). Death was more likely in patients living with HIV (hazard ratio [HR]=4.28, 95% confidence interval [CI] 1.26-12.86) and older patients (HR=1.08, 95%CI 1.05-1.12, increment of one year). Overall, 101/163 (62.0%) patients experienced long-term, relapse-free cure; of those, 101/122 (82.8%) patients with a known status (not lost to-follow-up or transferred out) at follow-up.
CONCLUSIONS: Under optimal management conditions leveraging individualized treatment regimens, long-term relapse-free cure from MDR/RR-TB is substantially higher than cure rates as defined by current treatment outcome definitions.

DOI: 10.1016/j.cmi.2023.02.013
PMID: 36842637

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

Curr Opin Pediatr. 2023 Feb 8. doi: 10.1097/MOP.0000000000001226. Online ahead of print.

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

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

efficient implementation in high TB burden countries while generating evidence to close current evidence gaps.

DOI: 10.1097/MOP.0000000000001226
PMID: 36749063

32. **Analysis of Dynamic Efficacy Endpoints of the Nix-TB Trial.**

Clin Infect Dis. 2023 Feb 21:ciad051. doi: 10.1093/cid/ciad051. Online ahead of print.

Solans BP(1)(2), Imperial MZ(1)(2), Olugbosi M(3), Savic RM(1)(2).

BACKGROUND: Safer, better, and shorter treatments for multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis (TB) are an urgent global health need. The phase 3 clinical trial Nix-TB (NCT02333799) tested a 6-month treatment of MDR and XDR-TB consisting of high-dose linezolid, bedaquiline, and pretomanid (BPaL). In this study, we investigate the relationship between the pharmacokinetic characteristics of the drugs, patient characteristics and efficacy endpoints from Nix-TB.
METHODS: Pharmacokinetic data were collected at weeks 2, 8, and 16. Efficacy endpoints including treatment outcomes, time to stable culture conversion, and longitudinal time to positivity in the mycobacterial growth indicator tube assay were each characterized using nonlinear mixed-effects modeling. Relationships between patient, treatment pharmacokinetics, and disease characteristics and efficacy endpoints were evaluated.
RESULTS: Data from 93 (85% of the total) participants were analyzed. Higher body mass index was associated with a lower incidence of unfavorable treatment outcomes. Median time to stable culture conversion was 3 months in patients with lower baseline burden compared with 4.5 months in patients with high baseline burden. Participants with minimal disease had steeper time to positivity trajectories compared with participants with high-risk phenotypes. No relationship between any drugs' pharmacokinetics (drug concentration or exposure metrics) and any efficacy outcomes was observed.
CONCLUSIONS: We have successfully described efficacy endpoints of a BPaL regimen from the Nix-TB trial. Participants with high-risk phenotypes significantly delayed time to culture conversion and bacterial clearance. The lack of a relationship between pharmacokinetic exposures and pharmacodynamic biomarkers opens the possibility to use lower, safer doses, particularly for toxicity-prone linezolid.

Infectious Diseases Society of America.

DOI: 10.1093/cid/ciad051
PMID: 36804834

Conflict of interest statement: Potential conflicts of interest. The authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

33. **Effectiveness of Bedaquiline Use Beyond Six Months in Patients with Multidrug-Resistant Tuberculosis.**

Am J Respir Crit Care Med. 2023 Feb 21. doi: 10.1164/rccm.202211-2125OC. Online ahead of print.

Trevisi L(1), Hernán MA(2), Mitnick CD(1)(3)(4), Khan U(5), Seung KJ(3)(4)(1), Rich ML(3)(4)(1), Bastard M(6), Huerga H(6), Melikyan N(6), Atwood S(3), Avaliani Z(7), Llanos F(8)(9), Manzur-Ul-Alam M(10), Zarli K(11), Binedgie AB(12), Adnan S(13), Melikyan A(14), Gelin A(15), Isani AK(16), Vetushko D(17), Daugarina Z(18), Nkundanyirazo P(19), Putri FA(20), Vilbrun C(21), Khan M(22), Hewison C(23), Khan PY(24), Franke MF(25).

RATIONALE: Current recommendations for the treatment of rifampin- and multidrug-resistant tuberculosis include bedaquiline used for six months or longer. Evidence is needed to inform the optimal duration of bedaquiline.
OBJECTIVES: We emulated a target trial to estimate the effect of three bedaquiline duration treatment strategies (6 months, 7-11 months, ≥ 12 months) on the probability of successful treatment among patients receiving a longer individualized regimen for multidrug-resistant tuberculosis.
METHODS: To estimate the probability of successful treatment, we implemented a three-step approach comprising cloning, censoring, and inverse-probability weighting.
MAIN RESULTS: The 1,468 eligible individuals received a median of four (IQR: 4-5) likely effective drugs. In 87.1% and 77.7%, this included linezolid and clofazimine, respectively. The adjusted probability of successful treatment (95% CI) was 0.85 (0.81, 0.88) for 6 months of BDQ, 0.77 (0.73, 0.81) for 7-11 months, and 0.86 (0.83, 0.88) for > 12 months. Compared with 6 months of bedaquiline, the ratio of treatment success (95% CI) was 0.91 (0.85, 0.96) for 7-11 months and 1.01 (0.96, 1.06) for > 12 months. Analyses that did not account for immortal time bias found a higher probability of successful treatment with > 12 months: ratio 1.09 (1.05, 1.14).
CONCLUSIONS: Bedaquiline use beyond six months did not increase the probability of successful treatment among patients receiving longer regimens that commonly

included new and repurposed drugs. When not properly accounted for, immortal person-time can bias estimate of effects of treatment duration. Future analyses should explore the effect of duration of bedaquiline and other drugs in subgroups with advanced disease and/or receiving less potent regimens.

DOI: 10.1164/rccm.202211-2125OC
PMID: 36802336

34. **Mechanisms of a Mycobacterium tuberculosis Active Peptide.**

Pharmaceutics. 2023 Feb 6;15(2):540. doi: 10.3390/pharmaceutics15020540.

Rao KU(1), Li P(2), Welinder C(3), Tenland E(1), Gourdon P(2)(4), Sturegård E(5), Ho JCS(6), Godaly G(1).

Multidrug-resistant tuberculosis (MDR) continues to pose a threat to public health. Previously, we identified a cationic host defense peptide with activity against Mycobacterium tuberculosis in vivo and with a bactericidal effect against MDR M. tuberculosis at therapeutic concentrations. To understand the mechanisms of this peptide, we investigated its interactions with live M. tuberculosis and liposomes as a model. Peptide interactions with M. tuberculosis inner membranes induced tube-shaped membranous structures and massive vesicle formation, thus leading to bubbling cell death and ghost cell formation. Liposomal studies revealed that peptide insertion into inner membranes induced changes in the peptides' secondary structure and that the membranes were pulled such that they aggregated without permeabilization, suggesting that the peptide has a strong inner membrane affinity. Finally, the peptide targeted essential proteins in M. tuberculosis, such as 60 kDa chaperonins and elongation factor Tu, that are involved in mycolic acid synthesis and protein folding, which had an impact on bacterial proliferation. The observed multifaceted targeting provides additional support for the therapeutic potential of this peptide.

DOI: 10.3390/pharmaceutics15020540
PMCID: PMC9958537
PMID: 36839864

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

35. **A host blood transcriptional signature differentiates multi-drug/rifampin-resistant tuberculosis (MDR/RR-TB) from drug susceptible tuberculosis: a pilot study.**

Mol Biol Rep. 2023 Feb 7. doi: 10.1007/s11033-023-08307-6. Online ahead of print.

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

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

DOI: 10.1007/s11033-023-08307-6
PMID: 36749527

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

Antimicrob Agents Chemother. 2023 Feb 6:e0142622. doi: 10.1128/aac.01426-22. Online ahead of print.

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

Moxifloxacin is included in some treatment regimens for drug-sensitive tuberculosis (TB) and multidrug-resistant TB (MDR-TB). Aiming to optimize dosing, we described moxifloxacin pharmacokinetic and MIC distribution in participants with MDR-TB. Participants enrolled at two TB hospitals in South Africa underwent intensive pharmacokinetic sampling approximately 1 to 6 weeks after treatment initiation. Plasma drug concentrations and clinical data were analyzed using nonlinear mixed-effects modeling with simulations to evaluate doses for different scenarios. We enrolled 131 participants (54 females), with median age of 35.7 (interquartile range, 28.5 to 43.5) years, median weight of 47 (42.0 to 54.0) kg, and median fat-free mass of 40.1 (32.3 to 44.7) kg; 79 were HIV positive, 29 of whom were on efavirenz-based antiretroviral therapy. Moxifloxacin pharmacokinetics were described with a 2-compartment model, transit absorption, and elimination via a liver compartment. We included allometry based on fat-free mass to estimate disposition parameters. We estimated an oral clearance for a typical patient to be 17.6 L/h. Participants treated with efavirenz had increased clearance, resulting in a 44% reduction in moxifloxacin exposure. Simulations predicted that, even at a median MIC of 0.25 (0.06 to 16) mg/L, the standard daily dose of 400 mg has a low probability of attaining the ratio of the area under the unbound concentration-time curve from 0 to 24 h to the MIC (fAUC0-24)/MIC target of >53, particularly in heavier participants. The high-dose WHO regimen (600 to 800 mg) yielded higher, more balanced exposures across the weight ranges, with better target attainment. When coadministered with efavirenz, moxifloxacin doses of up to 1,000 mg are needed to match these exposures. The safety of higher moxifloxacin doses in clinical settings should be confirmed.

DOI: 10.1128/aac.01426-22
PMID: 36744891

37. **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.

38. **Association Between Increased Linezolid Plasma Concentrations and the Development of Severe Toxicity in Multidrug-Resistant Tuberculosis Treatment.**

Clin Infect Dis. 2023 Feb 8;76(3):e947-e956. doi: 10.1093/cid/ciac485.

Eimer J(1), Fréchet-Jachym M(2), Le Dû D(2), Caumes E(3), El-Helali N(4), Marigot-Outtandy D(2)(5), Mechai F(6)(7), Peytavin G(8), Pourcher V(3), Rioux C(9), Yazdanpanah Y(9), Robert J(1)(10), Guglielmetti L(1)(10); LZDM group.

Collaborators: Aubry A, Bonnet I, Morel F, Veziris N, Lecorché E, Mougari F, Andrejak C, Bourgarit A, Klement E, Rivoire B, Thouvenin G, Tunesi S, Wicky M, Jaspard M, Alauzet C, Escaut L, Ellis-Corbet S, Bernard C, Roux AL.

BACKGROUND: Treatment of multidrug-resistant (MDR) tuberculosis with linezolid is characterized by high rates of adverse events. Evidence on therapeutic drug monitoring to predict drug toxicity is scarce. This study aimed to evaluate the association of linezolid trough concentrations with severe toxicity.
METHODS: We retrospectively assessed consecutive patients started on linezolid for MDR tuberculosis between 2011 and 2017. The primary outcome was severe mitochondrial toxicity (SMT) due to linezolid, defined as neurotoxicity or myelotoxicity leading to drug discontinuation. The impact of plasma linezolid trough concentrations >2 mg/L was assessed in multivariate Cox proportional hazards models including time-varying covariates.
RESULTS: SMT occurred in 57 of 146 included patients (39%) at an incidence rate of 0.38 per person-year (95% confidence interval, .30-.49). A maximum linezolid trough concentration >2 mg/L was detected in 52 patients (35.6%), while the mean trough concentration was >2 mg/L in 22 (15%). The adjusted hazard ratio for SMT was 2.35 (95% confidence interval, 1.26-4.38; P = .01) in patients with a mean trough concentration >2 mg/L and 2.63 (1.55-4.47; P < .01) for SMT after the first detection of a trough concentration >2 mg/L. In an exploratory analysis, higher maximum trough concentrations were dose-dependently associated with toxicity, while lowering elevated trough concentrations did not restore baseline risk.
CONCLUSIONS: Linezolid trough concentrations >2 mg/L are strongly associated with the development of severe treatment-emergent toxicity in patients treated for MDR tuberculosis. Pending further prospective evidence, an individual risk-benefit assessment on the continuation of linezolid treatment is warranted in any patient with trough concentrations >2 mg/L.

DOI: 10.1093/cid/ciac485
PMID: 35717636 [Indexed for MEDLINE]

Conflict of interest statement: Potential conflicts of interest. M. F. J. serves on the safety boards of the endTB (NCT 02754765) and endTB-Q (NCT 03896685) trials and has participated in prospective infectious sample collection for a study on tools for tuberculosis diagnosis (reference no. 18.12.27. 42115 for Cerba Xpert France). L. G. is a principal investigator in the aforementioned trials. G. P. has been a speaker for Gilead Sciences, Merck France, Pfizer, Takeda, Theratechnologies, and ViiV Healthcare and has received honoraria for lectures and presentations (payments to self). All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

39. **[Expert consensus on surgical treatment of multidrug-resistant and rifampicin-resistant pulmonary tuberculosis in China (2022 edition)].**

Zhonghua Jie He He Hu Xi Za Zhi. 2023 Feb 12;46(2):111-120. doi: 10.3760/cma.j.cn112147-20221222-00986.

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

Chinese Society for Tuberculosis, Chinese Medical Association.

The cure rate of multidrug-resistant and rifampicin-resistant pulmonary tuberculosis in the world is about 60%, and timely surgical intervention can increase the cure rate to more than 85%. The treatment of multidrug-resistant and rifampicin-resistant pulmonary tuberculosis requires multidisciplinary involvement of tuberculosis department, thoracic surgery department, imaging department, laboratory department and other disciplines to significantly reduce its morbidity and mortality. Although the World Health Organization has defined the role and status of surgery in the treatment of multidrug-resistant and rifampicin-resistant pulmonary tuberculosis, there are significant differences in the cognition and diagnosis and treatment methods of domestic clinicians on multidrug-resistant and rifampicin-resistant pulmonary tuberculosis. Therefore, it is urgent to develop expert consensus on surgical treatment of multidrug-resistant and rifampicin-resistant pulmonary tuberculosis for clinicians to learn from in clinical diagnosis and treatment practice. The Chinese Society for Tuberculosis,Chinese Medical Association organized experts in tuberculosis thoracic surgery to write the first draft of consensus based on the expert suggestion on surgical diagnosis and treatment of multidrug-resistant pulmonary tuberculosis written by the European Office of the World Health Organization in 2014 and the 2019 version of China's multidrug-resistant and rifampicin-resistant pulmonary tuberculosis expert consensus, and combined with China's national situation. This consensus systematically elaborated seven aspects, including surgical indications, contraindications to surgery, conditions and timing of surgery, surgical methods and indications of various surgical procedures, preoperative and postoperative chemotherapy, treatment of surgical complications, and perioperative management of patients with multidrug-resistant and rifampin-resistant pulmonary tuberculosis. After discussion and voting by experts, six recommendations were formed, aiming to provide reference for clinicians in the treatment of multidrug-resistant and rifampin-resistant pulmonary tuberculosis and further improve the standardized diagnosis and treatment level of multidrug-resistant and rifampin-resistant pulmonary tuberculosis in China.

DOI: 10.3760/cma.j.cn112147-20221222-00986
PMID: 36740370 [Indexed for MEDLINE]

40. **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.

41. **Evaluating Truenat Assay for the Diagnosis of Ocular Tuberculosis and Detection of Drug Resistance.**

Ocul Immunol Inflamm. 2023 Feb 1:1-7. doi: 10.1080/09273948.2023.2170888. Online ahead of print.

Sharma K(1), Sharma M(2), Ayyadurai N(3), Dogra M(3), Sharma A(4), Gupta V(3), Singh R(3), Gupta A(3).

BACKGROUND: Truenat MTB Plus assay was evaluated for diagnosing ocular

tuberculosis (OTB) and detecting multi-drug resistant (MDR) and extremely-drug resistant (XDR) OTB.
METHODS: A total of 75 vitreous fluid specimens [five confirmed OTB, 40 clinically suspected OTB and 30 controls] were subjected to Truenat MTB Plus, multiplex PCR, and Xpert Ultra. Chips of Truenat were used for detecting rifampicin, isoniazid, fluoroquinolone and bedaquiline resistance. The performance was compared against culture, composite reference standard, and gene sequencing.
RESULTS: The overall sensitivity of TruePlus, MPCR, and Ultra in diagnosing OTB was 66.6%, 73.3%, and 55.5%, respectively. Out of six cases with mutations in rpoB gene, RifR was detected in five by TrueRif and four by Ultra. Three MDR and one XDR-OTB were reported by Truenat.
CONCLUSION: Truenat assay along with its strategic chips is a rapid and reliable tool for diagnosis of OTB and detection of drug resistance, including MDR and XDR-OTB.Abbreviations: OTB: Ocular tuberculosis; XDR: Extremely drug resistant; Ultra: Xpert MTB/RIF Ultra; Xpert: Xpert MTB/RIF; PCR: polymerase chain reaction; NAATs: Nucleic acid amplification tests; MDR: Multi Drug Resistant; NSP: National Strategic plan for elimination of tuberculosis; FqR: Fluoroquinolone resistant; BdqR: bedaquiline resistant; TrueRif: Truenat MTB Rif Dx; TruePlus: Truenat Plus; INH: Isoniazid; DST: Drug susceptibility testing; MGIT: Mycobacterial growth indicator tube; CRF: Composite reference standard; PPV: positive predictive value; NPV: negative predictive value; EPTB: extrapulmonary tuberculosis; VF: vitreous fluid; DNA: deoxyribonucleic acid; ATT: antitubercular therapy; RifR: Rifampicin resistance; RifS: Rifampicin susceptible; RifI: Rifampicin indeterminate.

DOI: 10.1080/09273948.2023.2170888
PMID: 36726220

42. **[Annual progress on molecular biological diagnosis of tuberculosis 2022].**

Zhonghua Jie He He Hu Xi Za Zhi. 2023 Feb 12;46(2):176-182. doi: 10.3760/cma.j.cn112147-20221030-00857.

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

Liang C(1), Tang SJ(1).

Tuberculosis (TB) continues to be a global public health issue that threatens human health, and rapid and accurate pathogen detection is the key to early diagnosis and effective treatment. In recent years, the pathogenic diagnosis of tuberculosis is expanding from traditional bacteriological diagnosis to molecular diagnosis. In the past year, Xper MTB/RIF Ultra technology with good

diagnostic performance has been applied more often to the detection of non-respiratory samples, and Xpert XDR and second-generation linear probe technology provided more basis for early and accurate diagnosis of multidrug resistance; genome sequencing technology has also been developed and applied more often to the detection of non-culture sample detection, and the cost and time required for detection have been relatively reduced. Truenat technology, which is more suitable for primary care centers, is more widely used; new TB detection technologies, such as cell-free DNA testing and mass spectrometry, are also being developed and are expected to become important tools for early and rapid diagnosis of TB and drug-resistant TB. In this review, we synthesized the major research results of molecular biology diagnosis of tuberculosis around the world from 1st October 2021 to 30th September 2022, and comprehensively evaluated the advantages, disadvantages and current application of molecular biology detection technologies to provide a significant basis for clinical decision-making.

DOI: 10.3760/cma.j.cn112147-20221030-00857
PMID: 36740380 [Indexed for MEDLINE]

43. **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]

45. **"Crystal violet decolorization assay: a simplified colorimetric test for the rapid detection of multidrug-resistant Mycobacterium tuberculosis isolates".**

Microbes Infect. 2023 Feb 1:105108. doi: 10.1016/j.micinf.2023.105108. Online ahead of print.

Reghunath A(1), Shenoy VP(2), Kushal S(3), Pandey AK(4).

The increased prevalence of multi-drug resistant Mycobacterium tuberculosis is quite possibly the direst and most difficult task for the early diagnosis and treatment. A rapid, reliable, and inexpensive diagnostic method is the need of the hour. The current study on crystal violet decolorization assay explores the possibility to develop a rapid and simple detection method to detect multi-drug-resistant tuberculosis isolates by comparing the results with the traditional liquid culture drug susceptibility testing method based on their sensitivity, specificity, positive predictive value, and negative predictive value. 70 isolates were used for the study and were detected as multi-drug resistant, mono drug-resistant, and sensitive by using crystal violet decolourization assay and further compared with the results of DST and using H37Rv as the standard control strain. The sensitivity, specificity, positive predictive value, and negative predictive value of crystal violet decolorization assay (Rifampicin:100%, 94.60%, 100% and 82.40%; isoniazid:100%,94.10%,100%,86.40%) are calculated and the percentage were compared with the conventional liquid culture drug susceptibility testing for Mycobacterium tuberculosis using rifampicin and isoniazid. Crystal violet decolourization assay is rapid, reproducible, and doesn't require any highly experienced personal or sophisticated laboratory instruments for interpretation. This assay is found to be nearly as reliable as conventional liquid culture drug susceptibility testing and may thus be of great help in phenotypic confirmation of multi-drug resistant tuberculosis by providing results more rapidly.

DOI: 10.1016/j.micinf.2023.105108
PMID: 36736854

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

J Clin Microbiol. 2023 Feb 9:e0147822. doi: 10.1128/jcm.01478-22. Online ahead of print.

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

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

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

Cell. 2023 Feb 20:S0092-8674(23)00102-2. doi: 10.1016/j.cell.2023.01.043. Online ahead of print.

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

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

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PMID: 36827973

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

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

Antimicrob Agents Chemother. 2023 Feb 16;67(2):e0139922. doi: 10.1128/aac.01399-22. Epub 2023 Jan 9.

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.

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

49. **Simple and low-cost antibiotic susceptibility testing for Mycobacterium tuberculosis using screen-printed electrodes.**

Biotechnol Appl Biochem. 2023 Feb 4. doi: 10.1002/bab.2448. Online ahead of print.

Ghorbanpoor H(1)(2)(3)(4)(5), Akcakoca I(6), Norouz Dizaji A(2), Butterworth A(7), Corrigan D(7)(8), Kocagoz T(9)(10), Ebrahimi A(2)(4)(5), Avci H(3)(4)(5)(11), Dogan Guzel F(2).

One quarter of the global population is thought to be latently infected by

Mycobacterium tuberculosis (TB) with it estimated that 1 in 10 of those people will go on to develop active disease. Due to the fact that M. tuberculosis (TB) is a disease most often associated with low- and middle-income countries, it is critical that low-cost and easy-to-use technological solutions are developed, which can have a direct impact on diagnosis and prescribing practice for TB. One area where intervention could be particularly useful is antibiotic susceptibility testing (AST). This work presents a low-cost, simple-to-use AST sensor that can detect drug susceptibility on the basis of changing RNA abundance for the typically slow-growing M. tuberculosis (TB) pathogen in 96 h using screen-printed electrodes and standard molecular biology laboratory reactionware. In order to find out the sensitivity of applied sensor platform, a different concentration (108 -103 CFU/mL) of M. tuberculosis was performed, and limit of detection and limit of quantitation were calculated as 103.82 and 1011.59 CFU/mL, respectively. The results display that it was possible to detect TB sequences and distinguish antibiotic-treated cells from untreated cells with a label-free molecular detection. These findings pave the way for the development of a comprehensive, low-cost, and simple-to-use AST system for prescribing in TB and multidrug-resistant tuberculosis.

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PMID: 36738290

50. **[Evaluation of uniportal video-assisted thoracoscopic decortication in treatment of drug-resistant tuberculous empyema].**

Zhonghua Wai Ke Za Zhi. 2023 Feb 1;61(2):156-161. doi: 10.3760/cma.j.cn112139-20220519-00231.

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

Jiang YH(1), Shen L(1), Liu QB(1), Dai XY(1), Sheng J(1), Liu XY(1).

Objective: To examine the safety and efficacy of the uniportal video-assisted thoracoscopic decortication in treatment of drug-resistant tuberculosis empyema. Methods: From January 2018 to December 2020, 122 cases of tuberculous empyema treated by decortication in Department of Surgery, Wuhan Pulmonary Hospital were retrospectively analyzed, including 100 males and 22 females, aged(M(IQR)) 29.5(28.0) years (range: 13 to 70 years). According to the surgical approach and drug resistance, patients with drug-resistant tuberculosis who underwent uniportal video-assisted thoracoscopic decortication were included in group A (n=22), and those who underwent thoracotomy decortication were included in group

B (n=28). Drug-sensitive patients who underwent uniportal video-assisted thoracoscopic decortication were included in group C (n=72). There was no statistical difference in the baseline data of the three groups (P>0.05). The operation, early postoperative recovery, and prognosis-related indicators were compared among three groups by Kruskal-Wallis test and χ2 test by Mann-Whitney U test and Bonferroni method between groups A and B, groups A and C. Results: The intraoperative blood loss of group A, group B, and group C was 200(475) ml, 300(200) ml, and 225(300) ml, respectively. There was no significant difference in intraoperative hemorrhage (H=2.74, P=0.254) and treatment outcome (χ2=4.76, P=0.575) among the three groups. Compared with group B, the operation time of group A (302.5(187.5) minutes vs. 200.0(60.0) minutes, U=171.0, P=0.007) and postoperative pulmonary reexpansion duration (4.5(3.0) months vs. 3.0 (2.2) months, U=146.5, P=0.032) were longer, and the postoperative drainage duration (9.5(7.8) days vs. 13.0(10.0) days, U=410.0, P=0.044), and the postoperative hospitalization time (12.0(7.8) days vs. 14.5(4.8) days, U=462.2, P=0.020) were shorter. There was no significant difference in complications between group A and group B (63.6%(14/22) vs. 71.4%(20/28), χ2=0.34, P=0.558). Compared with group C, the postoperative drainage duration of group A (9.5(7.8) days vs. 7.0(4.0) days, U=543.5, P=0.031), the postoperative hospitalization time (12.0(7.8) days vs. 9.0(4.0) days, U=533.0, P=0.031) and postoperative pulmonary reexpansion duration (4.5(3.0) months vs. 3.0(2.0) months, U=961.5, P=0.001) were longer. The operation time (302.5(187.5) minutes vs. 242.5(188.8) minutes, U=670.5, P=0.278), and complications (63.6%(14/22) vs. 40.3%(29/72), χ2=3.70, P=0.054) were not different between group A and group C. Conclusions: For drug-resistant tuberculous empyema, the uniportal video-assisted thoracoscopic decortication can achieve the same good therapeutic effect as drug-sensitive tuberculous empyema, and it is as safe as thoracotomy. At the same time, it has the advantage of minimally invasive and can accelerate the early postoperative recovery of patients.

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PMID: 36720626 [Indexed for MEDLINE]

51. **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 [Indexed for MEDLINE]

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

52. **Stocking Practices of Anti-Tuberculosis Medications among Community Pharmacists and Patent Proprietary Medicine Vendors in Two States in Nigeria.**

Healthcare (Basel). 2023 Feb 15;11(4):584. doi: 10.3390/healthcare11040584.

Adepoju VA(1), Adelekan A(2), Oladimeji O(3)(4).

BACKGROUND: Evidence has shown that non-fixed-dose combination (non-FDC) anti-TB drugs could promote the spread of drug-resistant tuberculosis (DR-TB). We aimed to determine anti-TB medication stocking and dispensing practices among patent medicine vendors (PMVs) and community pharmacists (CPs) and their determinants.

METHOD: This was a cross-sectional study using a structured, self-administered questionnaire among 405 retail outlets (322 PMVs and 83 CPs) across 16 Lagos and Kebbi local government areas (LGAs) between June 2020 and December 2020. Data were analyzed with Statistical Program for Social Sciences (SPSS) for Windows version 17 (IBM Corp., Armonk, NY, USA). Chi-square test and binary logistic regression were used to assess the determinants of anti-TB medication stocking practices at a p-value of 0.05 or less for statistical significance.
RESULTS: Overall, 91%, 71%, 49%, 43% and 35% of the respondents reported stocking loose rifampicin, streptomycin, pyrazinamide, isoniazid and ethambutol tablets, respectively. From bivariate analysis, it was observed that being aware of directly observed therapy short course (DOTS) facilities (OR 0.48, CI 0.25-0.89, $p < 0.019$) and having previous training on TB (OR 0.32, CI 0.14-0.73, $p < 0.005$) reduced the odds of stocking anti-TB medication, while operating more than 1 shop (OR 3.32, CI 1.44-7.57, $p = 0.004$), having 3 or more apprentices (OR 5.31, CI 2.74-10.29, $p < 0.001$) and seeing over 20 clients/day (OR 3.02, CI 1.18-7.71, $p = 0.017$) increased the odds of stocking loose anti-TB medications. From multivariate analysis, it was observed that only the variable having three or more apprentices (OR 10.23, CI 0.10-0.49, $p = 0.001$) significantly increased the odds of stocking anti-TB medications.
CONCLUSIONS: The stocking of non-FDC anti-TB medications was high and largely determined by the number of apprentices among PMVs and CPs in Nigeria, and this may have serious implications for drug resistance development. However, the results linking the stocking of anti-TB to the number of apprentices should be interpreted cautiously as this study did not control for the level of sales in the pharmacies. We recommend that all capacity-building and regulatory efforts for PMVs and CPs in Nigeria should include not just the owners of retail premises but also their apprentices.

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PMCID: PMC9956350
PMID: 36833118

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

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

Biochemistry. 2023 Feb 7;62(3):710-721. doi: 10.1021/acs.biochem.2c00658. Epub 2023 Jan 19.

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.

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PMID: 36657084 [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 manuscript.

54. **Factors Associated with Tuberculosis Outcome in a Hyperendemic City in the North of Brazil.**

Healthcare (Basel). 2023 Feb 9;11(4):508. doi: 10.3390/healthcare11040508.

Costa GF(1), Garcez JCD(1), Marcos W(1), Ferreira ALDS(1), Andrade JAA(2), Rodrigues YC(3), Lima LNGC(1)(4), Conceição EC(5), Lima KVB(1)(4).

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Ananindeua city, State of Pará, North of Brazil, is a hyperendemic area for tuberculosis (TB), with a cure rate below the recommendation by the Brazilian Ministry of Health. We aimed to describe: (I) the TB incidence coefficient of Ananindeua municipality comparatively against Brazilian data; (II) TB treatment outcomes; (III) to compare the socioeconomic and epidemiological characteristics

of abandonment versus cure outcome; and (IV) to evaluate the risk factors associated with TB treatment abandonment in Ananindeua city, from 2017 to 2021. This is a retrospective, descriptive, and cross-sectional epidemiological study which used secondary TB entries. Data were analyzed by linear regression, descriptive statistics, and associations were made using the Chi-square test and G-test, followed by univariate and multivariate logistic regression analyses. Cure rates ranged from 28.7% to 70.1%, abandonment between 7.3% and 11.8%, deaths from the disease ranged from 0% to 1.6%, and drug-resistant tuberculosis (TB-DR) rates had frequencies from 0% to 0.9%. Patient transfer rates to other municipalities were between 4.9% and 12.5%. The multivariate analysis showed that alcohol is almost 2 times more likely to lead an individual to abandon treatment and use of illicit drugs was almost 3 times more likely. Individuals between 20 and 59 years of age were also more likely to abandon treatment almost twice as often. Finally, data obtained in the present report is of great relevance to strengthen epidemiological surveillance and minimize possible discrepancies between the information systems and the reality of public health in high endemicity areas.

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PMCID: PMC9957009
PMID: 36833042

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55. **Structure-Activity Relationship of Novel Pyrimidine Derivatives with Potent Inhibitory Activities against Mycobacterium tuberculosis.**

J Med Chem. 2023 Feb 23;66(4):2699-2716. doi: 10.1021/acs.jmedchem.2c01647. Epub 2023 Feb 3.

Li C(1), Tian X(2)(3)(4)(5), Huang Z(1), Gou X(1), Yusuf B(2)(3)(4)(5), Li C(1), Gao Y(2)(3)(4)(5), Liu S(1), Wang Y(6), Yang T(1), Liu Z(2)(3)(4)(5), Sun Q(1), Zhang T(2)(3)(4)(5), Luo Y(1).

Discovery of novel antitubercular drugs is an effective strategy against drug-resistant tuberculosis (TB). Our previous study has identified LPX-16j as a novel antitubercular compound. Herein, we perform a comprehensive structure-activity relationship (SAR) based on LPX-16j, indicating that the central pyrimidine ring moiety was crucial for the antitubercular activities of its derivatives, and replacing the naphthyl group with hydrophobic substitutes

was well tolerated. The representative derivative 5a exhibited potent activity against H37Ra, H37Rv, and clinical drug-resistant TB with minimum inhibitory concentration (MIC) values of 0.5-1.0 μg/mL. Meanwhile, 5a showed an acceptable safety in vivo and displayed a favorable oral bioavailability with a value of 40.7%. The differential scanning fluorescence, isothermal titration calorimetry, and molecular docking assays indicated that PknB could be one of the targets of compound 5a. Overall, this study identified 5a as a novel promising lead compound with the potential to develop candidates for the treatment of drug-resistant TB.

DOI: 10.1021/acs.jmedchem.2c01647
PMID: 36735271 [Indexed for MEDLINE]

56. **Congenital Tuberculosis After In Vitro Fertilization: A Case for Tuberculosis Screening of Women Evaluated for Infertility.**

Clin Infect Dis. 2023 Feb 8;76(3):e982-e986. doi: 10.1093/cid/ciac542.

Sands A(1)(2)(3), Santiago MT(2)(3)(4), Uduwana S(5), Glater-Welt L(2)(3)(6), Ezhuthachan ID(2)(7), Coscia G(2)(3)(7), Hayes L(2)(3)(8), Berry GJ(3)(9), Rubin LG(1)(2)(3), Hagmann SHF(1)(2)(3).

We report a case of multidrug-resistant congenital tuberculosis (TB) in an infant conceived by in vitro fertilization and review 22 additional infant-mother pairs in the literature. Females evaluated for infertility should be screened for TB risk, and those at risk require a TB-specific diagnostic evaluation before receiving assisted reproductive treatment.

DOI: 10.1093/cid/ciac542
PMID: 35788281 [Indexed for MEDLINE]

Conflict of interest statement: Potential conflicts of interest. The authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.