December Literature

1. **The efficacy of bedaquiline versus kanamycin in multi-drug resistant tuberculosis: A systematic scoping review.**

Health SA. 2021 Nov 29;26:1708. doi: 10.4102/hsag.v26i0.1708. eCollection 2021.

Singh L(1), Mathibe LJ(2), Bangalee V(1).

BACKGROUND: Drug-resistant tuberculosis (DR-TB) has become a serious cause of concern both on a global scale and in South Africa. It is associated with a lower successful treatment rate, thus creating a hurdle in achieving good treatment outcomes for patients.
AIM: The aim of this study was to compare the efficacy of the drug kanamycin, an injectable aminoglycoside, to bedaquiline, a newer oral drug used to treat DR-TB.
METHODS: PubMed and Google Scholar, both of which are online databases, were extensively searched using the necessary keywords so that studies that were relevant to the scoping review were retrieved. A data-charting list was developed to extract the needed data for this scoping review.
RESULTS: The main findings of the scoping review showed that bedaquiline was highly efficacious in the treatment of DR-TB, and that it was a valuable addition in the treatment of DR-TB. The findings of the study also showed that kanamycin does not have good efficacy against DR-TB. and its use extends the treatment of DR-TB.
CONCLUSION: It stands to reason that bedaquiline replaces kanamycin in the DR-TB drug regimen as it was shown to be more efficacious and patients experienced better treatment outcomes in a shorter period of time. There were also fewer adverse effects associated with bedaquiline as compared to kanamycin.
CONTRIBUTION: Bedaquiline-based DR-TB therapy is more efficacious than aminoglycoside-based regimens which include kanamycin.

DOI: 10.4102/hsag.v26i0.1708
PMCID: PMC8661289
PMID: 34917407

2. **The Treatment of Tuberculosis.**

Clin Pharmacol Ther. 2021 Dec;110(6):1455-1466. doi: 10.1002/cpt.2261. Epub 2021 Jun 5.

Peloquin CA(1), Davies GR(2)(3).

Tuberculosis (TB) remains a leading cause of infectious death worldwide, and poverty is a major driver. Clinically, TB presents as "latent" TB and active TB disease, and the treatment for each is different. TB drugs can display "early bactericidal activity (EBA)" and / or "sterilizing activity" (clearing persisters). Isoniazid is excellent at the former, and rifampin is excellent at the latter. Pyrazinamide and ethambutol complete the first-line regimen for drug-susceptible TB, each playing a specific role. Drug-resistant TB is an increasing concern, being met, in part, with repurposed drugs (including moxifloxacin, levofloxacin, linezolid, clofazimine, and beta-lactams) and new drugs (including bedaquiline, pretomanid, and delamanid). One challenge is to select drugs without overlapping adverse drug reaction profiles. QTc interval prolongation is one such concern, but to date, it has been manageable. Drug penetration into organism sanctuaries, such as the central nervous system, bone, and pulmonary TB cavities remain important challenges. The pharmacodynamics of most TB drugs can be described by the area under the curve (AUC) divided by the minimal inhibitory concentration (MIC). The hollow fiber infection model (HFIM) and various animal models (especially mouse and macaque) allow for sophisticated pharmacokinetic/pharmacodynamic experiments. These experiments may hasten the selection of the most potent, shortest possible regimens to treat even extremely drug resistant TB. These findings can be translated to humans by optimizing drug exposure in each patient, using therapeutic drug monitoring and dose individualization.

DOI: 10.1002/cpt.2261
PMID: 33837535 [Indexed for MEDLINE]

3. **Between Curing and Torturing: Burden of Adverse Reaction in Drug-Resistant Tuberculosis Therapy.**

Patient Prefer Adherence. 2021 Nov 23;15:2597-2607. doi: 10.2147/PPA.S333111. eCollection 2021.

Ausi Y(1)(2), Santoso P(3), Sunjaya DK(4), Barliana MI(1)(5).

Drug-resistant tuberculosis (DR-TB) requires prolonged and complex therapy which is associated with several adverse drug reactions (ADR). The burden of ADR can affect the quality of life (QoL) of patients that consists of physical, mental, and social well-being, and influences the beliefs and behaviors of patient related to treatment. This article reviews the burden of ADR and its association with QoL and adherence. We used PubMed to retrieve the relevant original research articles written in English from 2011 to 2021. We combined the

following keywords: "tuberculosis," "Drug-resistant tuberculosis," "Side Effect," "Adverse Drug Reactions," "Adverse Event," "Quality of Life," "Adherence," "Non-adherence," "Default," and "Loss to follow-up." Article selection process was unsystematic. We included 12 relevant main articles and summarized into two main topics, namely, 1) ADR and QoL (3 articles), and 2) ADR and therapy adherence (9 articles). The result showed that patients with ADR tend to have low QoL, even in the end of treatment. Although it was torturing, the presence of ADR does not always result in non-adherence. It is probably because the perception about the benefit of the treatment dominates the perceived barrier. In conclusion, burden of ADR generally tends to degrade QoL of patients and potentially influence the adherence. A comprehensive support from family, community, and healthcare provider is required to help patients in coping with the burden of ADR. Nevertheless, the regimen safety and efficacy improvement are highly needed.

DOI: 10.2147/PPA.S333111
PMCID: PMC8627322
PMID: 34848950

4. **Confronting and Coping with Multidrug-Resistant Tuberculosis: Life Experiences in Thailand.**

Qual Health Res. 2021 Nov 30:10497323211049777. doi: 10.1177/10497323211049777. Online ahead of print.

Numpong S(1), Kengganpanich M(2), Kaewkungwal J(1), Pan-Ngum W(1), Silachamroon U(3), Kasetjaroen Y(4), Lawpoolsri S(1).

In this article, we aimed to understand the life experiences of Thai persons diagnosed with multi-drug-resistant tuberculosis (MDR-TB). A qualitative study using a face-to-face in-depth interview was conducted at a hospital in Thailand which has the highest prevalence of MDR-TB in the country between January and February 2019. Twenty persons living with MDR-TB in Thailand were purposively selected to represent a variety of experiences based on different gender, ages, and treatment phases. Qualitative data were transcribed and thematic analysis was applied to identify common themes and sub-themes. The results indicated that all participants faced emotional difficulties, such as fear of death, fear of stigmatization, confusion, and sadness when first knowing of their diagnosis. Family and social support were the main ways that the patients coped with difficult situations. Suicidal ideas were more prevalent among patients with poor family support. Screening for mental health problems should be routinely performed in MDR-TB patients. Proper health education should be provided to patients and families to reduce emotional difficulties and stigmatization.

DOI: 10.1177/10497323211049777
PMID: 34845946

5. **The pipeline of new molecules and regimens against drug-resistant tuberculosis.**

J Clin Tuberc Other Mycobact Dis. 2021 Nov 5;25:100285. doi: 10.1016/j.jctube.2021.100285. eCollection 2021 Dec.

Black TA(1), Buchwald UK(1).

The clinical development and regulatory approval of bedaquiline, delamanid and pretomanid over the last decade brought about significant progress in the management of drug-resistant tuberculosis, providing all-oral regimens with favorable safety profiles. The Nix-TB and ZeNix trials of a bedaquiline - pretomanid - linezolid regimen demonstrated for the first time that certain forms of drug-resistant tuberculosis can be cured in the majority of patients within 6 months. Ongoing Phase 3 studies containing these drugs may further advance optimized regimen compositions. Investigational drugs in clinical development that target clinically validated mechanisms, such as second generation oxazolidinones (sutezolid, delpazolid, TBI-223) and diarylquinolines (TBAJ-876 and TBAJ-587) promise improved potency and/or safety compared to the first-in-class drugs. Compounds with novel targets involved in diverse bacterial functions such as cell wall synthesis (DrpE1, MmpL3), electron transport, DNA synthesis (GyrB), cholesterol metabolism and transcriptional regulation of ethionamide bioactivation pathways have advanced to early clinical studies with the potential to enhance antibacterial activity when added to new or established anti-TB drug regimens. Clinical validation of preclinical in vitro and animal model predictions of new anti-TB regimens may further improve the translational value of these models to identify optimal anti-TB therapies.

DOI: 10.1016/j.jctube.2021.100285
PMCID: PMC8593651
PMID: 34816020

6. **Epidemiological profile of multidrug-resistant and extensively drug-resistant Mycobacterium Tubrculosis among Congolese patients.**

Ann Clin Microbiol Antimicrob. 2021 Dec 17;20(1):84. doi: 10.1186/s12941-021-00488-x.

Elion Assiana DO(1)(2), Abdul JBPA(3), Linguissi LSG(1)(4), Epola M(3),

Vouvoungui JC(1)(2), Mabiala A(5), Biyogho CM(3), Ronald Edoa J(3), Adegbite BR(3), Adegnika AA(3)(6)(7), Elton L(8), Canseco JO(8), McHugh TD(8), Ahombo G(2), Ntoumi F(9)(10)(11).

BACKGROUND: There is paucity of data on the prevalence and distribution of multidrug- Resistant-Tuberculosis (MDR-TB) in the Republic of Congo. Among the challenges resides the implementation of a robust TB resistance diagnostic program using molecular tools. In resource limited settings there is a need to gather data to enable prioritization of actions. The objective of this study was is to implement molecular tools as a best of diagnosing MDR and XDR-TB among presumptive tuberculosis patients referred to reference hospital of Makelekele in Brazzaville, Republic of the Congo.
METHODS: We have conducted a cross-sectional study, including a total of 92 presumptive pulmonary tuberculosis patients and who had never received treatment recruited at the reference hospital of Makelekele from October 2018 to October 2019. The socio-demographic and clinical data were collected as well as sputum samples. Rifampicin resistance was investigated using Xpert (Cepheid) and second-line TB drugs Susceptibility testing were performed by the Brucker HAIN Line Probe Assay (GenoType MTBDRsl VER 2.0 assay) method.
RESULTS: From the 92 recruited patients, 57 (62%) were found positive for the Mycobacterium tuberculosis complex. The prevalence of rifampicin-resistant tuberculosis (RR-TB) was 9.8% (9/92) and importantly 2.2% were pre-XDR/XDR.
CONCLUSION: This study showed a high rate of rifampicin resistance and the presence of extensively drug-resistant tuberculosis in the study area in new patients. This study highlights the need for further studies of TB drug resistance in the country.

DOI: 10.1186/s12941-021-00488-x
PMID: 34920727

7. **Multi Drug Resistant Tuberculosis Clusters in Mpumalanga Province, South Africa, 2013-2016: A Spatial Analysis.**

Trop Med Int Health. 2021 Dec 7. doi: 10.1111/tmi.13708. Online ahead of print.

Mashamba MA(1), Tanser F(2)(3)(4), Afagbedzi S(5), Beke A(1).

OBJECTIVE: To identify spatial clusters with unusually high levels of MDR-TB which are highly unlikely to have arisen by chance in Mpumalanga Province, South Africa.
METHODS: Home addresses of all MDR-TB patients were collected from four MDR-TB facilities from 2013 to 2016. We mapped all addresses, linking them to the nearest ward with population estimates. A spatial analysis was conducted using

kernel density in ArcGIS to estimate and map the distribution of the disease and used Gertis-Ord Gi to test for significant clustering.
RESULTS: A total of 4,065 MDR-TB patients were mapped. Ten significant clusters (p-value < 0.05) were found across the province in six sub-districts: Mbombela, Nkomazi, Emalahleni, Govan Mbeki, Lekwa and Mkhondo. Mbombela has the highest number of significant clusters. The central region did not have any MDR-TB clusters.
CONCLUSION: There is clear evidence of MDR-TB clustering in Mpumalanga. This calls for concentrated TB prevention efforts and proper allocation of resources. Further investigations are needed to identify MDR-TB predictors.

DOI: 10.1111/tmi.13708
PMID: 34873790

8. **Culture conversion at six months in patients receiving bedaquiline- and delamanid-containing regimens for the treatment of multidrug-resistant tuberculosis.**

Int J Infect Dis. 2021 Dec;113 Suppl 1:S91-S95. doi: 10.1016/j.ijid.2021.03.075. Epub 2021 Apr 3.

Maretbayeva SM(1), Rakisheva AS(2), Adenov MM(3), Yeraliyeva LT(3), Algozhin YZ(1), Stambekova AT(1), Berikova EA(3), Yedilbayev A(4), Rich ML(5), Seung KJ(5), Issayeva AM(6).

Rifampicin-resistant/multidrug-resistant (RR/MDR) and extensively drug-resistant (XDR) strains of M. tuberculosis (TB) are serious public health problem in Kazakhstan. In 2012 and 2013, stringent regulatory authorities approved the first new TB drugs in fifty years, bedaquiline and delamanid, offering hope for more effective and less toxic MDR-TB treatment. The endTB Observational Study is a multi-country study that enrolled patients receiving a bedaquiline- or delamanid-containing regimen for RR/MDR-TB between 01 April 2015 and 30 September 2018. In Kazakhstan, 675 patients participated in the study; all had at least 6-months or longer of follow-up after the start of treatment. The present analysis focuses on endTB Observational Study patients living in Kazakhstan who had a positive baseline sputum culture (220 patients) and initiated a bedaquiline- or delamanid-containing regimen between February 1, 2016 and March 31, 2018. Of them, 195 (89%) of patients experienced culture conversion within six months.

DOI: 10.1016/j.ijid.2021.03.075

PMID: 33823277

9. **Telomere length and mitochondrial DNA copy number in multidrug-resistant tuberculosis.**

Tuberculosis (Edinb). 2021 Dec;131:102144. doi: 10.1016/j.tube.2021.102144. Epub 2021 Nov 10.

Freimane L(1), Barkane L(2), Igumnova V(3), Kivrane A(3), Zole E(3), Ranka R(4).

Multidrug resistant tuberculosis (MDR-TB) is a severe disease that requires prolonged chemotherapy and is associated with an increased probability of treatment failure and death. MDR-TB is a state of heightened oxidative stress and inflammation, which could be related to the aging-related processes and immunosenescence. We, therefore, tested the hypothesis that MDR-TB is associated with alterations in aging biomarkers in peripheral blood cells. We investigated 51 MDR-TB patients and 57 healthy individuals and carried out an analysis of covariance to assess the possible impact of different variables on biomarker perturbations. The results showed that MDR-TB patients had significantly reduced telomere length (TL) and increased mitochondrial DNA copy number (mtDNA CN) ($P < 0.05$) in comparison to the controls, and MDR-TB infection was the main influencing factor. Male sex and extrapulmonary TB strongly influenced mtDNA CN increment, and MDR-TB patients with normal weight had longer telomeres than those who were underweight ($P < 0.05$). In conclusion, the evidence for shorter telomeres and higher mtDNA CN in the peripheral blood cells of MDR-TB patients was obtained indicating the connection between MDR-TB and aging biomarkers. The observed associations highlight a complicated interplay between MDR-TB and immunosenescence, thus further studies are required to achieve full understanding.

DOI: 10.1016/j.tube.2021.102144
PMID: 34781086

10. **Aminoglycosides and Capreomycin in the Treatment of Multidrug-resistant Tuberculosis: Individual Patient Data Meta-analysis of 12 030 Patients From 25 Countries, 2009-2016.**

Clin Infect Dis. 2021 Dec 6;73(11):e3929-e3936. doi: 10.1093/cid/ciaa621.

Cegielski JP(1), Chan PC(2)(3), Lan Z(4), Udwadia ZF(5), Viiklepp P(6), Yim JJ(7), Menzies D(4).

BACKGROUND: As new drugs are developed for multidrug-resistant tuberculosis (MDR-TB), the role of currently used drugs must be reevaluated.
METHODS: We combined individual-level data on patients with pulmonary MDR-TB published during 2009-2016 from 25 countries. We compared patients receiving each of the injectable drugs and those receiving no injectable drugs. Analyses were based on patients whose isolates were susceptible to the drug they received. Using random-effects logistic regression with propensity score matching, we estimated the effect of each agent in terms of standardized treatment outcomes.
RESULTS: More patients received kanamycin (n = 4330) and capreomycin (n = 2401) than amikacin (n = 2275) or streptomycin (n = 1554), opposite to their apparent effectiveness. Compared with kanamycin, amikacin was associated with 6 more cures per 100 patients (95% confidence interval [CI], 4-8), while streptomycin was associated with 7 (95% CI, 5-8) more cures and 5 (95% CI, 4-7) fewer deaths per 100 patients. Compared with capreomycin, amikacin was associated with 9 (95% CI, 6-11) more cures and 5 (95% CI, 2-8) fewer deaths per 100 patients, while streptomycin was associated with 10 (95% CI, 8-13) more cures and 10 (95% CI, 7-12) fewer deaths per 100 patients treated. In contrast to amikacin and streptomycin, patients treated with kanamycin or capreomycin did not fare better than patients treated with no injectable drugs.
CONCLUSIONS: When aminoglycosides are used to treat MDR-TB and drug susceptibility test results support their use, streptomycin and amikacin, not kanamycin or capreomycin, are the drugs of choice.

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DOI: 10.1093/cid/ciaa621
PMCID: PMC8653626
PMID: 33124668

11. **Multidrug Resistant Tuberculosis With Simultaneously Acquired Drug Resistance to Bedaquiline and Delamanid.**

Clin Infect Dis. 2021 Dec 16;73(12):2329-2331. doi: 10.1093/cid/ciaa1064.

Yoshiyama T(1)(2), Takaki A(3), Aono A(3), Mitarai S(3), Okumura M(2), Ohta K(4), Kato S(1).

This study is the first to report a clinical case of simultaneously acquired resistance to bedaquiline (BDQ) and delamanid (DLM). Whole genome sequencing revealed 2 nucleotide insertions (Rv0678 and fbiC) in the Mycobacterium tuberculosis isolate. The minimum inhibitory concentrations for BDQ and DLM were 0.25 μg/mL and >2.0 μg/mL, respectively.

DOI: 10.1093/cid/ciaa1064
PMID: 32730621

12. **Population Pharmacokinetic and Concentration-QTc Analysis of Delamanid in Pediatric Participants with Multidrug-Resistant Tuberculosis.**

Antimicrob Agents Chemother. 2021 Nov 29:AAC0160821. doi: 10.1128/AAC.01608-21. Online ahead of print.

Sasaki T(1), Svensson EM(2)(3), Wang X(4), Wang Y(4), Hafkin J(4), Karlsson MO(2), Mallikaarjun S(4).

A population pharmacokinetic analysis of delamanid and its major metabolite DM-6705 was conducted to characterize the pharmacokinetics of delamanid and DM-6705 in pediatric participants with multidrug-resistant tuberculosis (MDR-TB). Data from participants between the ages of 0.67 to 17 years old, enrolled in 2 clinical trials, were utilized for the analysis. The final dataset contained 634 delamanid and 706 DM-6705 valid plasma concentrations from 37 children. A transit model with three compartments best described the absorption of delamanid. Two compartment models for each component with linear elimination were selected to characterize the disposition of delamanid and DM-6705, respectively. The covariates included in the model were body weight on apparent volume of distribution and apparent clearance (for both delamanid and DM-6705); formulation (dispersible vs film coated tablet) on mean absorption time; age, formulation, and dose on bioavailability of delamanid; age on the fraction of delamanid metabolized to DM-6705. Based on the simulations, doses for participants within different age/weight groups that result in delamanid exposure comparable to that in adults following the approved adult dose were calculated. By concentration-QTc (QTcB, QT corrected by Bazett's' formula) analysis, a significant positive correlation was detected with concentrations of DM-6705. However, the model-predicted upper bounds of the 90% confidence intervals of ΔQTc value were less than 10 ms at the simulated Cmax of DM-6705 following administration of maximum doses simulated. This suggests that the effect on the QT interval following the proposed dosing is unlikely to be clinically meaningful in children with MDR-TB who receive delamanid.

DOI: 10.1128/AAC.01608-21
PMID: 34843388

13. **Combining LAMP and Au-Nanoprobe to detect INH-RIF resistance accurately in**

tuberculosis: an evidence-based review.

J Infect Dev Ctries. 2021 Nov 30;15(11):1555-1568. doi: 10.3855/jidc.15188.

Habiburrahman M(1), Ariq H(2), Handayani RRD(3).

Approximately 1.41 million people die annually due to tuberculosis. One of the main problems in Tuberculosis eradication is the development of resistance to various antibiotics. However, current efforts to detect resistances face challenges such as limited equipment, budget, and time. This evidence-based review investigated loop-mediated isothermal amplification, an alternative molecular diagnostic tool with promising performance and applicability in developing countries, and its use combined with Au-Nanoprobe to detect antibiotic resistance in tuberculosis. The literature search was conducted through four databases (Proquest, EBSCOhost, Scopus, and Pubmed) for useful articles on loop-mediated isothermal amplification and Au-Nanoprobe in detecting tuberculosis and tuberculosis resistance. After filtering the result with inclusion and exclusion criteria, the search produced three papers that best answer the clinical question. Loop-mediated isothermal amplification amplifies a target sequence, and Au-Nanoprobe responds to the DNA specific to the target mutant, producing an observable color change. Loop-mediated isothermal amplification and Au-Nanoprobe showed 100% sensitivity and specificity in detecting rifampicin and isoniazid resistance. Another study investigated its viability to detect tuberculosis and found 98.2% sensitivity and 88.2% specificity. Combining loop-mediated isothermal amplification and Au-Nanoprobe had a shorter time to get results and should also be relatively cheaper because it does not need a high temperature to work and requires less equipment. In conclusion, loop-mediated isothermal amplification and Au-Nanoprobe can be used as an efficient and accurate method to detect isoniazid and rifampicin-resistant tuberculosis strains. The new technology is promising for developing countries due to their high disease burden but facing several healthcare barriers.

DOI: 10.3855/jidc.15188
PMID: 34898479

14. **Factors influencing treatment outcomes of tuberculosis patients attending health facilities in Galkayo Puntland, Somalia.**

J Public Health (Oxf). 2021 Dec 10;43(4):887-895. doi: 10.1093/pubmed/fdaa146.

Kassim SA(1)(2), Cote A(2), Kassim SM(3), Abbas M(4)(5), Baig MMFA(6), Ahmed AM(1), Hussein MM(6), Li X(1), Chen R(1)(7)(8).

AIM: This study evaluated the underlying factors associated with poor tuberculosis (TB) treatment outcomes among patients attending health care facilities in Galkayo, Puntland, Somalia.
METHODS: An institution-based cross-sectional study was conducted between 2016 and 2017 in three selected TB clinics. Data were collected from 400 TB patients, through medical record review and structured questionnaire. Multivariate logistic regression analyses were performed.
RESULTS: Of the 400 TB respondents, 57.3% were new cases, 12.3% had smear-negative TB and 12.5% had extrapulmonary TB. The median age was (35.66 ± 13.16) with majority being male (65.5%). Overall, 85% of patients were successfully treated, 9.7% failed and 5.3% defaulted. Multivariate analysis revealed that patient's body weight (odds ratio [OR]: 1.078); diabetes (OR: 8.022); family size (OR: 3.851); patients' delay in diagnosis (OR: 11.946); frequency of receiving anti-TB medication (OR: 9.068); smoker (OR: 5.723); category of patients (retreatment versus new, OR: 5.504; retreatment versus transfer in, OR: 4.957); health facilities (OR: 6.716) and treatment duration (OR: 132.091) were independent factors associated with poor TB outcomes.
CONCLUSIONS: Our findings highlight the need to improve TB services for vulnerable groups. They also emphasize the need for health system strengthening, public awareness and risk of treatment interruption. This may reduce both patients' delay in seeking care and TB treatment failure in Galkayo district.

DOI: 10.1093/pubmed/fdaa146
PMID: 32880632

15. **Cost-effectiveness of bedaquiline, pretomanid and linezolid for treatment of extensively drug-resistant tuberculosis in South Africa, Georgia and the Philippines.**

BMJ Open. 2021 Dec 3;11(12):e051521. doi: 10.1136/bmjopen-2021-051521.

Gomez GB(1)(2), Siapka M(3)(4), Conradie F(5), Ndjeka N(6), Garfin AMC(7), Lomtadze N(8), Avaliani Z(8), Kiria N(8), Malhotra S(9)(10), Cook-Scalise S(9)(11), Juneja S(9), Everitt D(9), Spigelman M(9), Vassall A(3).

OBJECTIVES: Patients with highly resistant tuberculosis have few treatment options. Bedaquiline, pretomanid and linezolid regimen (BPaL) is a new regimen shown to have favourable outcomes after six months. We present an economic evaluation of introducing BPaL against the extensively drug-resistant tuberculosis (XDR-TB) standard of care in three epidemiological settings.

DESIGN: Cost-effectiveness analysis using Markov cohort model.
SETTING: South Africa, Georgia and the Philippines.
PARTICIPANTS: XDR-TB and multidrug-resistant tuberculosis (MDR-TB) failure and treatment intolerant patients.
INTERVENTIONS: BPaL regimen. PRIMARY AND SECONDARY OUTCOME MEASURES: (1)
Incremental cost per disability-adjusted life years averted by using BPaL against standard of care at the Global Drug Facility list price. (2) The potential maximum price at which the BPaL regimen could become cost neutral.
RESULTS: BPaL for XDR-TB is likely to be cost saving in all study settings when pretomanid is priced at the Global Drug Facility list price. The magnitude of these savings depends on the prevalence of XDR-TB in the country and can amount, over 5 years, to approximately US$ 3 million in South Africa, US$ 200 000 and US$ 60 000 in Georgia and the Philippines, respectively. In South Africa, related future costs of antiretroviral treatment (ART) due to survival of more patients following treatment with BPaL reduced the magnitude of expected savings to approximately US$ 1 million. Overall, when BPaL is introduced to a wider population, including MDR-TB treatment failure and treatment intolerant, we observe increased savings and clinical benefits. The potential threshold price at which the probability of the introduction of BPaL becoming cost neutral begins to increase is higher in Georgia and the Philippines (US$ 3650 and US$ 3800, respectively) compared with South Africa (US$ 500) including ART costs.
CONCLUSIONS: Our results estimate that BPaL can be a cost-saving addition to the local TB programmes in varied programmatic settings.

DOI: 10.1136/bmjopen-2021-051521
PMCID: PMC8647530
PMID: 34862287

16. **Evaluation of the performance of the BD MAX MDR-TB test in the diagnosis of Mycobacterium tuberculosis complex in extrapulmonary and pulmonary samples.**

Expert Rev Mol Diagn. 2021 Dec;21(12):1361-1367. doi: 10.1080/14737159.2021.1997594. Epub 2021 Nov 16.

Sağıroğlu P(1), Atalay MA(1).

BACKGROUND: The BD MAX MDR-TB is a recently marketed molecular test for detecting Mycobacterium tuberculosis complex (MTC), rifampin, and isoniazid drug resistance.
RESEARCH DESIGN AND METHODS: This study aimed to evaluate the BD MAX MDR-TB test

performance in 933 extrapulmonary and 774 pulmonary samples.
RESULTS: Test MTC detecting sensitivity was 90.6%, 82.5%, and the specificity was 98.5%, 98.9%, in pulmonary and extrapulmonary samples, respectively. In smear-positive samples, sensitivity, and specificity were 100% for all samples. However, in smear-negative samples, the test's sensitivity and specificity were 82.3%, 98.5% in pulmonary samples, and 76.7%, 98.9% in extrapulmonary samples. Test sensitivity in detecting isoniazid resistance was 71.4%, specificity 96.8%, and in detecting rifampin resistance was 100%, specificity 93.9%, respectively.
CONCLUSIONS: BD MAX MDR-TB is a reliable, rapid, user-friendly test for detecting MTC in extrapulmonary and pulmonary samples and its resistance toward isoniazid and rifampin. It can be used as an alternative to the Xpert system assays.

DOI: 10.1080/14737159.2021.1997594
PMID: 34689662

17. **Effectiveness and Cardiac Safety of Bedaquiline-Based Therapy for Drug-Resistant Tuberculosis: A Prospective Cohort Study.**

Clin Infect Dis. 2021 Dec 6;73(11):2083-2092. doi: 10.1093/cid/ciab335.

Brust JCM(1), Gandhi NR(2)(3), Wasserman S(4), Maartens G(4)(5), Omar SV(6)(7), Ismail NA(6)(7), Campbell A(2), Joseph L(1), Hahn A(1), Allana S(2), Hernandez-Romieu AC(3), Zhang C(1), Mlisana K(8), Viljoen CA(9), Zalta B(10), Ebrahim I(4), Franczek M(2), Master I(11), Ramangoaela L(12), Te Riele J(13), Meintjes G(4).

BACKGROUND: Bedaquiline improves treatment outcomes in patients with rifampin-resistant (RR) tuberculosis but prolongs the QT interval and carries a black-box warning from the US Food and Drug Administration. The World Health Organization recommends that all patients with RR tuberculosis receive a regimen containing bedaquiline, yet a phase 3 clinical trial demonstrating its cardiac safety has not been published.
METHODS: We conducted an observational cohort study of patients with RR tuberculosis from 3 provinces in South Africa who received regimens containing bedaquiline. We performed rigorous cardiac monitoring, which included obtaining electrocardiograms in triplicate at 4 time points during bedaquiline therapy. Participants were followed up until the end of therapy or 24 months. Outcomes included final tuberculosis treatment outcome and QT interval prolongation (QT prolongation), defined as any QT interval corrected by the Fridericia method (QTcF) >500 ms or an absolute change from baseline (ΔQTcF) >60 ms.
RESULTS: We enrolled 195 eligible participants, of whom 40% had extensively drug-resistant tuberculosis. Most participants (97%) received concurrent clofazimine. Of the participants, 74% were cured or successfully completed treatment, and outcomes did not differ by human immunodeficiency virus status.

QTcF continued to increase throughout bedaquiline therapy, with a mean increase (standard deviation) of 23.7 (22.7) ms from baseline to month 6. Four participants experienced a QTcF >500 ms and 19 experienced a ΔQTcF >60 ms. Older age was independently associated with QT prolongation. QT prolongation was neither more common nor more severe in participants receiving concurrent lopinavir-ritonavir.
CONCLUSIONS: Severe QT prolongation was uncommon and did not require permanent discontinuation of either bedaquiline or clofazimine. Close monitoring of the QT interval may be advisable in older patients.

DOI: 10.1093/cid/ciab335
PMCID: PMC8664482
PMID: 33882121

18. **Cost of TB services in healthcare facilities in Kenya (No 3).**

Int J Tuberc Lung Dis. 2021 Dec 1;25(12):1028-1034. doi: 10.5588/ijtld.21.0129.

Kairu A(1), Orangi S(1), Oyando R(1), Kabia E(1), Nguhiu P(1), Ong Ang O J(2), Mwirigi N(3), Laurence YV(4), Kitson N(4), Garcia Baena I(5), Vassall A(4), Barasa E(6), Sweeney S(4), Cunnama L(7).

BACKGROUND: The reduction of Kenya´s TB burden requires improving resource allocation both to and within the National TB, Leprosy and Lung Disease Program (NTLD-P). We aimed to estimate the unit costs of TB services for budgeting by NTLD-P, and allocative efficiency analyses for future National Strategic Plan (NSP) costing.METHODS: We estimated costs of all TB interventions in a sample of 20 public and private health facilities from eight counties. We calculated national-level unit costs from a health provider´s perspective using bottom-up (BU) and top-down (TD) approaches for the financial year 2017-2018 using Microsoft Excel and STATA v16.RESULTS: The mean unit cost for passive case-finding (PCF) was respectively US$38 and US$60 using the BU and TD approaches. The unit BU and TD costs of a 6-month first-line treatment (FLT) course, including monitoring tests, was respectively US$135 and US$160, while those for adult drug-resistant TB (DR-TB) treatment was respectively US$3,230.28 and US$3,926.52 for the 9-month short regimen. Intervention costs highlighted variations between BU and TD approaches. Overall, TD costs were higher than BU, as these are able to capture more costs due to inefficiency (breaks/downtime/leave).CONCLUSION: The activity-based TB unit costs form a comprehensive cost database, and the costing process has built-in capacity within the NTLD-P and international TB research networks, which will inform future TB budgeting processes.

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PMCID: PMC8675875
PMID: 34886934

19. **Correlating genetic mutations with isoniazid phenotypic levels of resistance in Mycobacterium tuberculosis isolates from patients with drug-resistant tuberculosis in a high burden setting.**

Eur J Clin Microbiol Infect Dis. 2021 Dec;40(12):2551-2561. doi: 10.1007/s10096-021-04316-0. Epub 2021 Jul 23.

Pinhata JMW(1), Brandao AP(2)(3), Mendes FF(2), Rabello MCDS(4), Ferrazoli L(2), de Oliveira RS(2).

We analysed mutations in katG, inhA and rpoB genes, and isoniazid phenotypic resistance levels in Mycobacterium tuberculosis isolates from drug-resistant TB patients from São Paulo state, Brazil. Isolates resistant to the critical concentration of isoniazid in MGIT (0.1 µg/mL) were screened for mutations in katG 315 codon, inhA promoter region and rpoB RRDR by MTBDRplus assay and subjected to determination of isoniazid resistance levels by MGIT 960. Discordances were resolved by Sanger sequencing. Among the 203 isolates studied, 109 (54%) were isoniazid-monoresistant, 47 (23%) MDR, 29 (14%) polydrug-resistant, 12 (6%) pre-XDR and 6 (3%) XDR. MTBDRplus detected isoniazid mutations in 75% (153/203) of the isolates. Sequencing of the entire katG and inhA genes revealed mutations in 18/50 wild-type isolates by MTBDRplus (10 with novel mutations), resulting in a total of 32/203 (16%) isolates with no mutations detected. 81/83 (98%) isolates with katG 315 mutations alone had intermediate resistance. Of the 66 isolates with inhA C-15T mutation alone, 51 (77%) showed low-level, 14 (21%) intermediate and 1 (2%) high-level resistance. 5/6 (83%) isolates with mutations in both katG and inhA had high-level resistance. Inferred mutations corresponded to 22% (16/73) of all mutations found in rpoB. Mutations detected in katG regions other than codon 315 in this study might be potential new isoniazid resistance markers and could explain phenotypic resistance in some isolates without katG and inhA classic mutations. In our setting, 16% of isoniazid-resistant isolates, some with high-level resistance, presented no mutations either in katG or inhA.

DOI: 10.1007/s10096-021-04316-0
PMID: 34297229

20. **Accelerating development of new shorter TB treatment regimens in anticipation of a resurgence of multi-drug resistant TB due to the COVID-19 pandemic.**

Int J Infect Dis. 2021 Dec;113 Suppl 1:S96-S99. doi: 10.1016/j.ijid.2021.02.067. Epub 2021 Mar 10.

Tiberi S(1), Vjecha MJ(2), Zumla A(3), Galvin J(4), Migliori GB(5), Zumla A(6).

The WHO 2020 global TB Report estimates that in 2019 there were an estimated 500,000 cases of multi-drug resistant TB (MDR-TB) of which only 186,772 MDR-TB cases were diagnosed, and positive treatment outcomes were achieved in 57% of them. These data highlight the need for accelerating and improving MDR-TB screening, diagnostic, treatment and patient follow-up services. The last decade has seen three new TB drugs being licensed; bedaquiline, delamanid and pretomanid, and combinations these new, existing and repurposed drugs are leading to improved cure rates. The all oral six month WHO regimen for MDR-TB is more tolerable, has higher treatment success rates and lower mortality. However, the unprecedented ongoing COVID-19 pandemic is having major direct and indirect negative impacts on health services overall, including national TB programs and TB services. This adds further to longstanding challenges for tackling MDR-TB such as cost, rollout of diagnostics and drugs, and implementation of latest WHO guidelines for MDR-TB. In light of COVID-19 disruption of TB services, it is anticipated the numbers of MDR-TB cases will rise in 2021 and 2022 and will affect treatment outcomes further. Investing more in development of new TB drugs and shorter MDR-TB treatment regimens is required in anticipation of emerging drug resistance to new TB drug regimens. There is an urgent need for protecting current investments in TB services, sustaining gains being made in TB control and accelerating roll out of TB diagnostic and treatment services.

DOI: 10.1016/j.ijid.2021.02.067
PMCID: PMC7944856
PMID: 33713815

21. **Emergence of additional drug resistance during treatment of multidrug-resistant tuberculosis in China: a prospective cohort study.**

Clin Microbiol Infect. 2021 Dec;27(12):1805-1813. doi: 10.1016/j.cmi.2021.04.001. Epub 2021 Apr 23.

Hu Y(1), Zheng X(1), Davies Forsman L(2), Ning Z(3), Chen C(4), Gao Y(1), Zhang Z(3), Lu W(4), Werngren J(5), Bruchfeld J(2), Hoffner S(6), Xu B(7).

OBJECTIVES: Little is known about how additional second-line drug resistance

emerges during multidrug-resistant tuberculosis (MDR-TB) treatment. The present study aimed to investigate the influence of microevolution, exogenous reinfection and mixed infection on second-line drug resistance during the recommended 2-year MDR-TB treatment.
METHODS: Individuals with MDR-TB were enrolled between 2013 and 2016 in a multicentre prospective observational cohort study and were followed up for 2 years until treatment completion. Whole-genome sequencing (WGS) was applied for serial Mycobacterium tuberculosis isolates from study participants throughout the treatment, to study the role of microevolution, exogenous reinfection and mixed infection in the development of second-line drug resistance.
RESULTS: Of the 286 enrolled patients with MDR-TB, 63 (22.0%) M. tuberculosis isolates developed additional drug resistance during the MDR-TB treatment, including 5 that fulfilled the criteria of extensively drug-resistant TB. By comparing WGS data of serial isolates retrieved from the patients throughout treatment, 41 (65.1%) of the cases of additional second-line drug resistance were the result of exogenous reinfection, 18 (28.6%) were caused by acquired drug resistance, i.e. microevolution, while the remaining 4 (6.3%) were caused by mixed infections with drug-resistant and drug-susceptible strains. In multivariate analysis, previous TB treatment (adjusted hazard ratio (aHR) 2.51, 95% CI 1.51-4.18), extensive disease on chest X-ray (aHR 3.39, 95% CI 2.03-5.66) and type 2 diabetes mellitus (aHR 4.00, 95% CI 2.22-7.21) were independent risk factors associated with the development of additional second-line drug resistance.
CONCLUSIONS: A large proportion of additional second-line drug resistance emerging during MDR-TB treatment was attributed to exogenous reinfection, indicating the urgency of infection control in health facilities as well as the need for repeated drug susceptibility testing throughout MDR-TB treatment.

DOI: 10.1016/j.cmi.2021.04.001
PMID: 33895338

22. **New silver(I) phosphino complexes: Evaluation of their potential as prospective agents against Mycobacterium tuberculosis.**

J Inorg Biochem. 2021 Dec 3;227:111683. doi: 10.1016/j.jinorgbio.2021.111683. Online ahead of print.

Maldonado YD(1), Scalese G(2), Manieri KF(3), Pavan FR(3), Aguirre Méndez LD(4), Gambino D(5).

Despite being a preventable and curable disease, Tuberculosis (TB) is the

world's top infectious killer. Development of new drugs is urgently needed. In this work, the synthesis and characterization of new silver(I) complexes, that include N'-[(E)-(pyridine-2-ylmethylene)pyrazine-2-carbohydrazide, HPCPH, as main ligand and substituted aryl-phosphines as auxiliary ligands, is reported. HPCPH was synthesized from pyrazinoic acid, the active metabolite of the first-line antimycobacterial drug pyrazinamide. Complexes [Ag(HPCPH)(PPh3)2]OTf (1), [Ag(HPCPH)((P(p-tolyl)3)2]OTf (2) and [Ag(HPCPH)(P(p-anisyl)3)2]OTf (3) were characterized in solid state and in solution by elemental analysis and FTIR and NMR spectroscopies (OTftriflate). Crystal structures of (1,2) were determined by XRD. The Ag atom is coordinated to azomethine and pyridine nitrogen atoms of HPCPH ligand and to the phosphorous atom of each aryl-phosphine co-ligand. Although HPCPH did not show activity, the Ag(I) compounds demonstrated activity against Mycobacterium tuberculosis (MTB), H37Rv strain, and multi-drug resistant clinical isolates (MDR-TB). Globally, results showed that the compounds are not only effective against the sensitive strain, but are more potent against MDR-TB than antimycobacterial drugs used in therapy. The compounds showed low to moderate selectivity index values (SI) towards the bacteria, using MRC-5 cells (ATCC CCL-171) as mammalian cell model. Interaction with DNA was explored to get insight into the potential mechanism of action against the pathogen. No significant interaction was detected, allowing to discard this biomolecule as a potential molecular target. Compound 1 was identified as a hit compound (MIC90 2.23 μM; SI 4.4) to develop further chemical modifications in the search for new drugs.

DOI: 10.1016/j.jinorgbio.2021.111683
PMID: 34896768

23. **Cost of TB services in the public and private sectors in Georgia (No 2).**

Int J Tuberc Lung Dis. 2021 Dec 1;25(12):1019-1027. doi: 10.5588/ijtld.21.0176.

Chikovani I(1), Shengelia N(1), Marjanishvili N(1), Gabunia T(2), Khonelidze I(3), Cunnama L(4), Garcia Baena I(5), Kitson N(6), Sweeney S(6), Vassall A(6), Laurence YV(6).

BACKGROUND: Patient-centred care along with optimal financing of inpatient and outpatient services are the main priorities of the Georgia National TB Programme (NTP). This paper presents TB diagnostics and treatment unit cost, their comparison with NTP tariffs and how the study findings informed TB financing policy.METHODS: Top-down (TD) and bottom-up (BU) mean unit costs for TB interventions by episode of care were calculated. TD costs were compared with NTP tariffs, and variations in these and the unit costs cost composition between public and private facilities was assessed.RESULTS: Outpatient interventions

costs exceeded NTP tariffs. Unit costs in private facilities were higher compared with public providers. There was very little difference between per-day costs for drug-susceptible treatment and NTP tariffs in case of inpatient services. Treatment day financing exceeded actual costs in the capital (public facility) for drug-resistant TB, and this was lower in the regions.CONCLUSION: Use of reliable unit costs for TB services at policy discussions led to a shift from per-day payment to a diagnosis-related group model in TB inpatient financing in 2020. A next step will be informing policy decisions on outpatient TB care financing to reduce the existing gap between funding and costs.

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PMCID: PMC8675873
PMID: 34886933

24. **Efflux pump gene expression study using RNA-seq in multidrug-resistant TB.**

Int J Tuberc Lung Dis. 2021 Dec 1;25(12):974-981. doi: 10.5588/ijtld.21.0117.

Lee JJ(1), Kang HY(2), Lee WI(3), Cho SY(2), Kim YJ(2), Lee HJ(4).

BACKGROUND: The mechanism underlying kanamycin (KM) resistance in Mycobacterium tuberculosis is not well understood, although efflux pump proteins are thought to play a role. This study used RNA-seq data to investigate changes in the expression levels of efflux pump genes following exposure to KM.METHODS: RNA expression of efflux pump and regulatory genes following exposure to different concentrations of KM (minimum inhibitory concentration MIC 25 and MIC50) in rrs wild-type strain and rrs A1401G mutated strain were compared with the control group.RESULTS: The selected strains had differential RNA expression patterns. Among the 71 putative efflux pump and regulatory genes, 46 had significant fold changes, and 12 genes (Rv0842, Rv1146, Rv1258c, Rv1473, Rv1686c, Rv1687c, Rv1877, Rv2038c, Rv3065, Rv3197a, Rv3728 and Rv3789) that were overexpressed following exposure to KM were thought to contribute to drug resistance. Rv3197A (whiB7) showed a distinct fold change based on the concentration of KM.CONCLUSION: The significant changes in the expression of the efflux pump and regulatory genes following exposure to KM may provide insights into the identification of a new resistance mechanism.

DOI: 10.5588/ijtld.21.0117
PMID: 34886926

25. **Temporal trends of pharmacologic treatments for tuberculosis and multidrug resistant tuberculosis following dissemination of treatment guidelines in South Korea.**

J Microbiol Immunol Infect. 2021 Nov 30:S1684-1182(21)00267-X. doi: 10.1016/j.jmii.2021.11.007. Online ahead of print.

Jeong HE(1), Choi J(2), Oh IS(1), Son H(3), Jang SH(4), Jung SY(5), Shin JY(6).

BACKGROUND/PURPOSE(S): The World Health Organization (WHO) released treatment guidelines for multidrug resistant tuberculosis (MDR-TB) in 2008, with subsequent revisions in 2011; Korea disseminated corresponding guidelines in 2011 and 2014, respectively. Thus, we aimed to investigate the temporal trends of and the updated guideline's impact on the prescription patterns of anti-TB drugs.
METHODS: We conducted a time-series study using Korea's nationwide healthcare database (2007-2015), where patients with TB or MDR-TB were included. Only anti-TB drugs prescribed during the intensive phase of treatment for TB (two months) or MDR-TB (eight months) were assessed. We estimated the annual utilization of TB treatment regimens and the relative difference (RD) in the proportion of MDR-TB treatment medications between the following periods: before the first Korean guideline (June 2008 to March 2011); between the first and revised guidelines (April 2011 to July 2014); after the revised guideline (August 2014 to December 2015).
RESULTS: Of 3523 TB (mean age 54.1 years; male 56.8%) patients, treatment regimens for TB complied with guideline recommendations as >80% of patients received either quadruple (mean 66.8%) or triple (14.5%) therapy of first-line anti-TB drugs. Following the WHO's guideline update, prescription patterns changed accordingly among 111 MDR-TB (mean age 46.0 years; male 67.6%) patients, as use of pyrazinamide (RD +20.3%) and prothionamide (+11.5%) increased (recommended to be compulsory), and streptomycin (-43.1%) decreased (ototoxicity risks).
CONCLUSIONS: Anti-TB drug prescription patterns for both TB and MDR-TB well reflected WHO's treatment guideline as well as corresponding domestic guidelines of South Korea.

DOI: 10.1016/j.jmii.2021.11.007
PMID: 34896029

26. **Exposure-safety analysis of QTc interval and transaminase levels following bedaquiline administration in patients with drug-resistant tuberculosis.**

CPT Pharmacometrics Syst Pharmacol. 2021 Dec;10(12):1538-1549. doi: 10.1002/psp4.12722. Epub 2021 Oct 22.

Tanneau L(1), Svensson EM(1)(2), Rossenu S(3), Karlsson MO(1).

Bedaquiline (BDQ) has shown great value in the treatment of multidrug-resistant tuberculosis (MDR-TB) in recent years. However, exposure-safety relationships must be explored to extend the use of BDQ. Two reported safety findings for BDQ are prolongation of the QTc interval and elevation of transaminase levels. In this study, we investigated the potential relationships between BDQ and/or its main metabolite (M2) pharmacokinetic (PK) metrics and QTcF interval or transaminase levels in patients with MDR-TB using the approved dose regimen. Data from 429 patients with MDR-TB from two phase IIb studies were analyzed via nonlinear mixed-effects modeling. Individual model-predicted concentrations and summary PK metrics were evaluated, respectively, in the QTcF interval and transaminase level exposure-response models. Investigation of further covariate effects was performed in both models. M2 concentrations were found to be responsible for the drug-related QTcF increase in a model accounting for circadian rhythm patterns, time on study, effect of concomitant medication with QT liability, and patient demographics. Simulations with the final model suggested that doses higher than the approved dose (leading to increased M2 concentrations) are not expected to lead to a critical QTcF interval increase. No exposure-safety relationship could be described with transaminase levels despite previous reports of higher levels in patients treated with BDQ. The developed longitudinal models characterized the role of M2 concentrations in QTc interval prolongation and found no concentration dependency for transaminase level elevation, together suggesting that BDQ exposure at the high end of the observed range may not be associated with a higher risk of safety events.

DOI: 10.1002/psp4.12722
PMID: 34626526

27. **Key factors influencing multidrug-resistant tuberculosis in patients under anti-tuberculosis treatment in two centres in Burundi: a mixed effect modelling study.**

BMC Public Health. 2021 Nov 23;21(1):2142. doi: 10.1186/s12889-021-12233-2.

Iradukunda A(1)(2)(3), Ndayishimiye GP(4), Sinarinzi D(4), Odjidja EN(5)(6), Ntakaburimvo N(4), Nshimirimana I(7), Izere C(8).

BACKGROUND: Despite the World Health Organization efforts to expand access to the tuberculosis treatment, multidrug resistant tuberculosis (MDR-TB) remains a major threat. MDR-TB represents a challenge for clinicians and staff operating in national tuberculosis (TB) programmes/centres. In sub-Saharan African countries including Burundi, MDR-TB coexists with high burden of other

communicable and non-communicable diseases, creating a complex public health situation which is difficult to address. Tackling this will require targeted public health intervention based on evidence which well defines the at-risk population. In this study, using data from two referral anti-tuberculosis in Burundi, we model the key factors associated with MDR-TB in Burundi.
METHODS: A case-control study was conducted from 1stAugust 2019 to 15th January 2020 in Kibumbu Sanatorium and Bujumbura anti-tuberculosis centres for cases and controls respectively. In all, 180 TB patients were selected, comprising of 60 cases and 120 controls using incidence density selection method. The associated factors were carried out by mixed effect logistic regression. Model performance was assessed by the Area under Curve (AUC). Model was internally validated via bootstrapping with 2000 replications. All analysis were done using R Statistical 3.5.0.
RESULTS: MDR-TB was more identified among patients who lived in rural areas (51.3%), in patients' residence (69.2%) and among those with a household size of six or more family members (59.5%). Most of the MDR-TB cases had already been under TB treatment (86.4%), had previous contact with an MDR-TR case (85.0%), consumed tobacco (55.5%) and were diabetic (66.6 %). HIV prevalence was 32.3 % in controls and 67.7 % among cases. After modelling using mixed effects, Residence of patients (aOR= 1.31, 95%C: 1.12-1.80), living in houses with more than 6 family members (aOR= 4.15, 95% C: 3.06-5.39), previous close contact with MDR-TB (aOR= 6.03, 95% C: 4.01-8.12), history of TB treatment (aOR= 2.16, 95% C: 1.06-3.42), tobacco consumption (aOR = 3.17 ,95% C: 2.06-5.45) and underlying diabetes' (aOR= 4.09,95% CI = 2.01-16.79) were significantly associated with MDR-TB. With 2000 stratified bootstrap replicates, the model had an excellent predictive performance, accurately predicting 88.15% (95% C: 82.06%-92.8%) of all observations. The coexistence of risk factors to the same patients increases the risk of MDR-TB occurrence. TB patients with no any risk factors had 17.6% of risk to become MDR-TB. That probability was respectively three times and five times higher among diabetic and close contact MDR-TB patients.
CONCLUSION: The relatively high TB's prevalence and MDR-TB occurrence in Burundi raises a cause for concern especially in this context where there exist an equally high burden of chronic diseases including malnutrition. Targeting interventions based on these identified risk factors will allow judicious channel of resources and effective public health planning.

DOI: 10.1186/s12889-021-12233-2
PMCID: PMC8609742
PMID: 34814876 [Indexed for MEDLINE]

28. **Risk factors associated with drug-resistant tuberculosis in prisons in São Paulo State, Brazil (2006-2016).**

J Infect Dev Ctries. 2021 Nov 30;15(11):1661-1669. doi: 10.3855/jidc.14843.

De Almeida Crispim J(1), Arroyo LH(2), Zamboni Berra T(2), Lima Dos Santos F(2), Limirio Souza LL(2), Alves YM(2), Vieira Ramos AC(2), Inomata Bruce AT(2), Yamamura M(3), Rolim Scholze A(2), Pinto de Andrade HL(2), Meneguetti Pieri F(4), Carvalho Pinto I(2), Fredemir Palha P(2), Arcêncio RA(2).

INTRODUCTION: Prisons are high-risk settings for drug-resistant tuberculosis because the prevalence of the tuberculosis (TB) is much higher than in the general population. This study to investigated the factors associated with drug-resistant tuberculosis in prisons in the state of São Paulo, Brazil.
METHODOLOGY: Retrospective cohort of drug-resistant TB cases for incarcerated people in São Paulo state, reported in the Tuberculosis Patient Control System between 2006 and 2016. To analyze the factors associated with drug-resistant TB, the backward method (likelihood ratio) was used, determining the adjusted odds ratio and respective 95%CI coefficients. Multiple models were proposed to adjust for potential confusion and interaction. The best fit model was selected based on the lowest Akaike information criterion coefficient.
RESULTS: In total, 473 drug-resistant tuberculosis cases were reported in the prison population of São Paulo state, the majority were male. The cases that presented negative results for sputum smear and sputum culture had, respectively, an aOR=0.6 and aOR=0.16 for drug-resistant tuberculosis in relation to the cases with positive results. The cases where the patient had AIDS and reported alcoholism, respectively, an aOR=1.47 and aOR=1.60 for drug-resistant TB. Individuals with a background treatment history for TB presented a stronger association with drug-resistant tuberculosis, aOR=35.08.
CONCLUSIONS: Sputum spear, sputum culture, chest X-ray, AIDS, alcoholism and background treatment history for TB were factors associated with resistance to antituberculosis drugs among prisoners. This is useful for the implementation of disease control measures related to the detection and monitoring of cases in the prison system.

DOI: 10.3855/jidc.14843
PMID: 34898494

29. **Performance of GenoType MTBDRsl assay for detection of second-line drugs and ethambutol resistance directly from sputum specimens of MDR-TB patients in Bangladesh.**

PLoS One. 2021 Dec 16;16(12):e0261329. doi: 10.1371/journal.pone.0261329. eCollection 2021.

Rahman SMM(1), Nasrin R(1), Rahman A(1)(2), Ahmed S(1), Khatun R(1), Uddin MKM(1), Rahman MM(3), Banu S(1).

BACKGROUND: Rapid and early detection of drug susceptibility among multidrug-resistant tuberculosis (MDR-TB) patients could guide the timely initiation of effective treatment and reduce transmission of drug-resistant TB. In the current study, we evaluated the diagnostic performance of GenoType MTBDRsl (MTBDRsl) ver1.0 assay for detection of resistance to ofloxacin (OFL), kanamycin (KAN) and ethambutol (EMB), and additionally the XDR-TB among MDR-TB patients in Bangladesh.
METHODS: The MTBDRsl assay was performed directly on 218 smear-positive sputum specimens collected from MDR-TB patients and the results were compared with the phenotypic drug susceptibility testing (DST) performed on solid Lowenstein-Jensen (L-J) media. We also analyzed the mutation patterns of gyrA, rrs, and embB genes for detection of resistance to OFL, KAN and EMB, respectively.
RESULTS: The sensitivity and specificity of the MTBDRsl compared to phenotypic L-J DST were 81.8% (95% CI, 69.1-90.9) and 98.8% (95% CI, 95.6-99.8), respectively for OFL (PPV: 95.7% & NPV: 94.1%); 65.1% (95% CI, 57.5-72.2) and 86.7% (95% CI, 73.2-94.9), respectively for EMB (PPV: 94.9% & NPV: 39.4%); and 100% for KAN. The diagnostic accuracy of KAN, OFL and EMB were 100, 94.5 and 69.6%, respectively. Moreover, the sensitivity, specificity and diagnostic accuracy of MtBDRsl for detection of XDR-TB was 100%. The most frequently observed mutations were at codon D94G (46.8%) of gyrA gene, A1401G (83.3%) of rrs gene, and M306V (41.5%) of the embB gene.
CONCLUSION: Considering the excellent performance in this study we suggest that MTBDRsl assay can be used as an initial rapid test for detection of KAN and OFL susceptibility, as well as XDR-TB directly from smear-positive sputum specimens of MDR-TB patients in Bangladesh.

DOI: 10.1371/journal.pone.0261329
PMCID: PMC8675706
PMID: 34914803

30. **The whole-genome sequencing in predicting Mycobacterium tuberculosis drug susceptibility and resistance in Papua, Indonesia.**

BMC Genomics. 2021 Nov 22;22(1):844. doi: 10.1186/s12864-021-08139-3.

Maladan Y(1), Krismawati H(2), Wahyuni T(2), Tanjung R(2), Awaludin K(3), Audah KA(4), Parikesit AA(5).

BACKGROUND: Tuberculosis is one of the deadliest disease caused by Mycobacterium tuberculosis. Its treatment still becomes a burden for many countries including Indonesia. Drug resistance is one of the problems in TB treatment. However, a development in the molecular field through Whole-genome sequencing (WGS) can be used as a solution in detecting mutations associated with TB- drugs. This investigation intended to implement this data for supporting the scientific community in deeply understanding any TB epidemiology and evolution in Papua along with detecting any mutations in genes associated with TB-Drugs.
RESULT: A whole-genome sequencing was performed on the random samples from TB Referral Laboratory in Papua utilizing MiSeq 600 cycle Reagent Kit (V3). Furthermore, TBProfiler was used for genome analysis, RAST Server was employed for annotation, while Gview server was applied for BLAST genome mapping and a Microscope server was implemented for Regions of Genomic Plasticity (RGP). The largest genome of M. tuberculosis obtained was at the size of 4,396,040 bp with subsystems number at 309 and the number of coding sequences at 4326. One sample (TB751) contained one RGP. The drug resistance analysis revealed that several mutations associated with TB-drug resistance existed. In details, mutations of rpoB gene which were identified as S450L, D435Y, H445Y, L430P, and Q432K had caused the reduced effectiveness of rifampicin; while the mutases in katG (S315T), kasA (312S), inhA (I21V), and Rv1482c-fabG1 (C-15 T) genes had contributed to the resistance in isoniazid. In streptomycin, the resistance was triggered by the mutations in rpsL (K43R) and rrs (A514C, A514T) genes, and, in Amikacin, its resistance was led by mutations in rrs (A514C) gene. Additionally, in Ethambutol and Pyrazinamide, their reduced effectiveness was provoked by embB gene mutases (M306L, M306V, D1024N) and pncA (W119R).
CONCLUSIONS: The results from whole-genome sequencing of TB clinical sample in Papua, Indonesia could contribute to the surveillance of TB-drug resistance. In the drug resistance profile, there were 15 Multi Drugs Resistance (MDR) samples. However, Extensively Drug-resistant (XDR) samples have not been found, but samples were resistant to only Amikacin, a second-line drug.

DOI: 10.1186/s12864-021-08139-3
PMCID: PMC8607662
PMID: 34802420 [Indexed for MEDLINE]

31. **Whole-genome sequencing as a tool for studying the microevolution of drug-resistant serial Mycobacterium tuberculosis isolates.**

Tuberculosis (Edinb). 2021 Dec;131:102137. doi: 10.1016/j.tube.2021.102137. Epub 2021 Oct 4.

de Lourdes do Carmo Guimarães Diniz J(1), von Groll A(2), Unis G(3), Dalla-Costa

ER(4), Rosa Rossetti ML(5), Vianna JS(2), Ramos DF(2), Reis AJ(2), Bartolomeu Halicki PC(2), Rheingantz Scaini JL(6), Castillos de Ibrahim das Neves Y(2), Phelan J(7), Gomes AR(7), Campino S(7), Machado KDS(6), Werhli AV(6), Pain A(8), Clark TG(7), Perdigão J(9), Viveiros M(10), Portugal I(9), Almeida Silva PE(2).

Treatment of drug-resistant tuberculosis requires extended use of more toxic and less effective drugs and may result in retreatment cases due to failure, abandonment or disease recurrence. It is therefore important to understand the evolutionary process of drug resistance in Mycobacterium tuberculosis. We here in describe the microevolution of drug resistance in serial isolates from six previously treated patients. Drug resistance was initially investigated through phenotypic methods, followed by genotypic approaches. The use of whole-genome sequencing allowed the identification of mutations in the katG, rpsL and rpoB genes associated with drug resistance, including the detection of rare mutations in katG and mixed populations of strains. Molecular docking simulation studies of the impact of observed mutations on isoniazid binding were also performed. Whole-genome sequencing detected 266 single nucleotide polymorphisms between two isolates obtained from one patient, suggesting a case of exogenous reinfection. In conclusion, sequencing technologies can detect rare mutations related to drug resistance, identify subpopulations of resistant strains, and identify diverse populations of strains due to exogenous reinfection, thus improving tuberculosis control by guiding early implementation of appropriate clinical and therapeutic interventions.

DOI: 10.1016/j.tube.2021.102137
PMID: 34673379

32. **Genetic diversity and drug susceptibility of Mycobacterium tuberculosis in a city with a high prevalence of drug resistant tuberculosis from Southeast of Mexico.**

BMC Infect Dis. 2021 Nov 30;21(1):1202. doi: 10.1186/s12879-021-06904-z.

Zenteno-Cuevas R(1)(2), Munro-Rojas D(3), Pérez-Martínez D(4)(5), Fernandez-Morales E(4)(6), Jimenez-Ruano AC(6), Montero H(4), Escobar L(7), de Igartua E(7), Trigos Á(8), Fuentes-Dominguez J(7).

BACKGROUND: Mexico is on the top five countries with the highest number of TB cases in America continent, nevertheless, information about genotypes circulating is practically unknown. Considering the above this study aims to characterize the genetic diversity of TB in the city of Veracruz, México.
METHODS: A cross-sectional study was conducted among positive smear samples from patients living in Veracruz City, samples were cultured, and first-line drug

profiles determined. Genotyping was made by spoligotyping and MIRU-VNTR 24 loci. Associations of lineages, clusters, and variables were also analyzed.
RESULTS: Among the 202 isolates analyzed resistance to at least one drug was observed in 60 (30%) isolates and 41(20%) were multidrug-resistant. Three major lineages were identified: L4/Euro-American (88%), L1/Indo-Oceanic (9%), and L2/East Asian (3%). The Euro-American lineage included more than six sublineages, the most abundant were: H (32%), T (23%), LAM (18%), and X (12%). 140 isolates (70%) were placed in 42 SITs patterns.
CONCLUSIONS: These results provide the first baseline data on the genetic structure of TB in the city of Veracruz. Sublineages H, X and LAM were predominant; however, it was founded an important diversity of genotypes that could contribute to the dispersion of TB and explain the high prevalence. This information might be useful for the development of further interventions to reduce impact of TB.

DOI: 10.1186/s12879-021-06904-z
PMCID: PMC8630842
PMID: 34847856 [Indexed for MEDLINE]

33. **Adjunctive surgery versus medical treatment among patients with cavitary multidrug-resistant tuberculosis.**

Eur J Cardiothorac Surg. 2021 Dec 1;60(6):1279-1285. doi: 10.1093/ejcts/ezab337.

Vashakidze SA(1)(2), Gogishvili SG(1), Nikolaishvili KG(1), Avaliani ZR(1), Chandrakumaran A(3), Gogishvili GS(1), Magee M(4), Blumberg HM(5), Kempker RR(5).

OBJECTIVES: Surgical resection is recommended as adjunctive treatment for multidrug-resistant (MDR) tuberculosis (TB) in certain scenarios; however, data are limited. We sought to evaluate the impact of surgery by comparing TB outcomes among patients with cavitary disease who received medical versus combined medical and surgical treatment.
METHODS: A cohort of all patients with cavitary MDR or extensively drug-resistant (XDR) TB treated in Tbilisi, Georgia, between 2008 and 2012. Patients meeting indications for surgery underwent adjunctive resection in addition to medical treatment. We compared TB outcomes (proportions achieving cure/complete) among patients who received adjunctive surgery to those who received medical treatment alone using an adjusted robust Poisson regression.
RESULTS: Among 408 patients, 299 received medical treatment alone and 109 combined medical and surgical treatment. Patients in the non-surgical group were older and had higher rates of tobacco and alcohol use and bilateral disease compared to the surgical group. Patients in the surgical group had higher rates

of XDR disease (28% vs 15%). Favourable outcomes were higher among the surgical versus non-surgical group cohort (76% vs 41%). After adjusting for multiple factors, the association between adjunctive resection and favourable outcome remained (adjusted risk ratio 1.6, 95% confidence interval 1.3-2.0); the relationship was also observed in secondary models that excluded patients with bilateral disease (contraindication for surgery) and patients receiving <6 months of treatment. Major postoperative complications occurred among 8 patients (7%) with no postoperative mortality.
CONCLUSIONS: Adjunctive surgery is safe and may improve the effectiveness of treatment among select patients with cavitary MDR- and XDR-TB.

DOI: 10.1093/ejcts/ezab337
PMCID: PMC8643477
PMID: 34297819

34. **Xpert MTB/RIF Use Is Associated With Earlier Treatment Initiation and Culture Conversion Among Patients With Sputum Smear-Negative Multidrug-Resistant Tuberculosis.**

Open Forum Infect Dis. 2021 Nov 6;8(12):ofab551. doi: 10.1093/ofid/ofab551. eCollection 2021 Dec.

Kipiani M(1)(2), Graciaa DS(3), Buziashvili M(1), Darchia L(4), Avaliani Z(1), Tabagari N(5), Mirtskhulava V(6), Kempker RR(3).

BACKGROUND: Although rapid molecular diagnostic tests for tuberculosis (TB) have decreased detection time of Mycobacterium tuberculosis and drug resistance, whether their use improves clinical care and outcomes is uncertain. To address these knowledge gaps, we evaluated whether use of the Xpert MTB/RIF assay impacts treatment and clinical outcome metrics among patients treated for sputum smear-negative multidrug-resistant (MDR)-TB.
METHODS: We conducted a retrospective cohort study of adult patients initiating treatment for sputum smear-negative MDR-TB at the National Center for Tuberculosis and Lung Diseases in Tbilisi, Georgia from 2011 to 2016. The Xpert MTB/RIF was introduced in Georgia in 2010 and implemented into programmatic use in 2014. Exposure was availability of an Xpert result at time of diagnosis. Time to second-line treatment initiation, sputum culture conversion, and end-of-treatment outcomes were determined. Time to event was compared using a Cox proportional hazards model.
RESULTS: Among 151 patients treated for sputum smear-negative MDR-TB (96% culture positive), the Xpert was utilized in the clinical management of 78 (52%) patients and not used in 73 (48%). An adjusted analysis controlling for

potential confounders found that patients in the Xpert group had shorter median time to second-line treatment (13 vs 56 days; adjusted hazard ratio [aHR], 10.21; P < .0001) and culture conversion (61 vs 93 days; aHR, 1.93; P < .001). There was no difference in treatment outcomes.
CONCLUSIONS: Use of the Xpert in the management of sputum smear-negative MDR-TB decreases time to second-line therapy and sputum culture conversion, providing evidence of its clinical impact and supporting its programmatic utility.

DOI: 10.1093/ofid/ofab551
PMCID: PMC8643647
PMID: 34877367

35. **Accuracy of an amplicon-sequencing nanopore approach to identify variants in tuberculosis drug-resistance-associated genes.**

Microb Genom. 2021 Dec;7(12). doi: 10.1099/mgen.0.000740.

Mariner-Llicer C(1), Goig GA(2)(3), Zaragoza-Infante L(4), Torres-Puente M(1), Villamayor L(5), Navarro D(6)(7), Borras R(6)(7), Chiner-Oms Á(1), Comas I(1)(8).

A rapid and accurate diagnostic assay represents an important means to detect Mycobacterium tuberculosis, identify drug-resistant strains and ensure treatment success. Currently employed techniques to diagnose drug-resistant tuberculosis include slow phenotypic tests or more rapid molecular assays that evaluate a limited range of drugs. Whole-genome-sequencing-based approaches can detect known drug-resistance-conferring mutations and novel variations; however, the dependence on growing samples in culture, and the associated delays in achieving results, represents a significant limitation. As an alternative, targeted sequencing strategies can be directly performed on clinical samples at high throughput. This study proposes a targeted sequencing assay to rapidly detect drug-resistant strains of M. tuberculosis using the Nanopore MinION sequencing platform. We designed a single-tube assay that targets nine genes associated with drug resistance to seven drugs and two phylogenetic-determining regions to determine strain lineage and tested it in nine clinical isolates and six sputa. The study's main aim is to calibrate MinNION variant calling to detect drug-resistance-associated mutations with different frequencies to match the accuracy of Illumina (the current gold-standard sequencing technology) from both culture and sputum samples. After calibrating Nanopore MinION variant calling, we demonstrated 100% agreement between Illumina WGS and our MinION set up to detect known drug resistance and phylogenetic variants in our dataset. Importantly, other variants in the amplicons are also detected, decreasing the

recall. We identify minority variants and insertions/deletions as crucial bioinformatics challenges to fully reproduce Illumina WGS results.

DOI: 10.1099/mgen.0.000740
PMID: 34919513

36. **Value of routine whole genome sequencing for Mycobacterium tuberculosis drug resistance detection.**

Int J Infect Dis. 2021 Dec;113 Suppl 1:S48-S54. doi: 10.1016/j.ijid.2021.03.033. Epub 2021 Mar 19.

Lam C(1), Martinez E(2), Crighton T(2), Furlong C(3), Donnan E(3), Marais BJ(4), Sintchenko V(5).

Routine whole genome sequencing (WGS) of pathogens is becoming more feasible as sequencing costs decrease and access to benchtop sequencing equipment and bioinformatics pipelines increases. This study examined the added value gained from implementing routine WGS of all Mycobacterium tuberculosis isolates in New South Wales, Australia. Drug resistance markers inferred from WGS data were compared to commercial genotypic drug susceptibility testing (DST) assays and conventional phenotypic DST in all isolates sequenced between 2016 and 2019. Of the 1107 clinical M. tuberculosis isolates sequenced, 29 (2.6%) were multi-drug resistant (MDR); most belonged to Beijing (336; 30.4%) or East-African Indian (332; 30%) lineages. Compared with conventional phenotypic DST, WGS identified an additional 1% of isolates which were likely drug resistant, explained by mutations previously associated with treatment failure and mixed bacterial populations. However, WGS provided a 20% increase in drug resistance detection in comparison with commercial genotypic assays by identifying mutations outside of the classic resistance determining regions in rpoB, inhA, katG, pncA and embB genes. Gains in drug resistance detection were significant ($p = 0.0137$, paired t-test), but varied substantially for different phylogenetic lineages. In low incidence settings, routine WGS of M. tuberculosis provides better guidance for person-centered management of drug resistant tuberculosis than commercial genotypic assays.

DOI: 10.1016/j.ijid.2021.03.033
PMID: 33753222

37. **Drug Resistance in Children with Central Nervous System Tuberculosis from a Tertiary Care Center in Mumbai.**

J Trop Pediatr. 2021 Dec 8;67(6):fmab098. doi: 10.1093/tropej/fmab098.

Mane SS(1), Janardhanan J(1), Pustake M(1), Ali MK(1), Khan GI(1).

INTRODUCTION: Central Nervous System tuberculosis (CNS-TB) is the most lethal form of extra-pulmonary TB, especially in children. In this study, we have discussed patterns of drug resistance in pediatric CNS-TB.
MATERIALS AND METHODS: Prospective observational study conducted on 100 children at a tertiary care center. Diagnosed cases of CNS-TB were enrolled. GeneXpert MTB/RIF was used upfront for diagnosis, and in cases where TB MGIT culture was positive, a phenotypic Drug Susceptibility Test (DST) was done. Patients were divided into resistant to at least one drug (DR) and drug-susceptible (DS). Various parameters were compared between these groups.
RESULTS: Mean age of participants was 5.84 ± 3.5 years, with a male-to-female ratio of 1.08 : 1; 14% of children had drug-resistant CNS TB (DR-CNS-TB). A higher proportion of children previously treated for TB were associated with drug resistance ($p = 0.009$), and those with disseminated TB also had a higher drug resistance ($p = 0.002$). Apart from this, the DR and DS groups had no statistically significant differences in demographic, clinical or epidemiological parameters.
CONCLUSIONS: Previous history of being treated for TB and disseminated TB was an independent risk factor for DR-CNS-TB. Ensuring proper adherence and compliance to anti-tubercular treatment could help in preventing the emergence of DR TB.

DOI: 10.1093/tropej/fmab098
PMID: 34918167

38. **High-dose gatifloxacin-based shorter treatment regimens for MDR/RR-TB.**

Int J Infect Dis. 2021 Nov 30:S1201-9712(21)00886-9. doi: 10.1016/j.ijid.2021.11.037. Online ahead of print.

Nie Q(1), Tao L(2), Li Y(3), Chen N(4), Chen H(4), Zhou Y(4), Wang Y(4), Chen H(5), Tang Q(4), Wang X(6), Huang C(7), Yang C(8).

SETTING: The shorter treatment regimen (STR) for multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB) has achieved successful outcomes in many countries. However, there are few studies on high-dose gatifloxacin-based STR with adverse drug reactions (ADRs) and management.
DESIGN: A prospective observational study was conducted with MDR/RR-TB patients who were treated with a standardized 9 or 12 - month regimen: including gatifloxacin (Gfx), clofazimine (Cfz), ethambutol (EMB), and pyrazinamide (PZA),

and supplemented by amikacin (Am), isoniazid (INH), and prothionamide (Pto) during an intensive phase of 4 or 6 - month. Monitored ADRs monthly until treatment completion and then followed up every three months for one year.
RESULTS: Among the 42 eligible patients, 35 (83.3%) completed treatment successfully, 1 (2.4%) lost to follow-up (LTFU), and 6 (14.3%) failed due to ADRs, with no death. The most important ADR was drug-induced liver damage, which occurred in 24 out of 42 (57.1%) patients and resulted in 4 (9.5%) failed treatments and 4 (9.5%) adjusted treatments. QT interval prolongation occurred in 17 out of 42 (40.5%) patients, 9 (21.4%) of them with the corrected QT interval according to Fridericia (QTcF) > 500 ms resulting in 7 (16.7%) adjusted treatments.
CONCLUSIONS: This study confirmed the effectiveness of the high-dose gatifloxacin-based STR but severe ADRs, especially hepatotoxicity and QT interval prolongation should never be ignored.

DOI: 10.1016/j.ijid.2021.11.037
PMID: 34861398

39. **Association between body mass index and newly diagnosed drug-resistant pulmonary tuberculosis in Shandong, China from 2004 to 2019.**

BMC Pulm Med. 2021 Dec 6;21(1):399. doi: 10.1186/s12890-021-01774-2.

Song WM(#)(1)(2), Guo J(#)(1)(3)(4), Xu TT(1)(3), Li SJ(1)(2), Liu JY(5), Tao NN(6)(7), Liu Y(1), Zhang QY(1)(2), Liu SQ(1)(2), An QQ(1)(2), Li YF(1), Yu CB(8), Dong JH(9), Li HC(10)(11).

BACKGROUND: Drug-resistant tuberculosis (DR-TB), obesity, and malnutrition are growing public health problems in the world. However, little has discussed the impact of different BMI status on the emergence of TB drug resistance. We aimed to explore the drug-resistant profiles of DR-TB and its clinical predictors among underweight, overweight or obesity population.
METHODS: 8957 newly diagnosed TB cases with drug susceptibility results and BMI data in Shandong China, from 2004 to 2019 were enrolled. Multivariable and univariable logistic regression models were applied to investigate the impact of BMI on different drug-resistance. Clinical predicators and drug-resistant profiles of DR-TB among obesity, underweight, normal TB group were also described.
RESULTS: Among 8957 TB cases, 6417 (71.64%) were normal weight, 2121 (23.68%) were underweight, 373 (4.16%) were overweight, and 46 (0.51%) were obese. The proportion of drug resistance and co-morbidity among normal weight, underweight, overweight, obese TB groups were 18.86%/18.25%/20.38%/23.91% (DR-TB), 11.19%/11.74%/9.65%/17.39% (mono-resistant tuberculosis, MR-TB),

3.41%/3.06%/5.36%/0.00% (multidrug resistant tuberculosis, MDR-TB), 4.21%/3.39%/5.36%/6.52% (polydrug resistant tuberculosis, PDR-TB), 10.57%/8.44%/19.57%/23.91% (co-morbidity), respectively. Compared with normal weight group, underweight were associated with lower risk of streptomycin-related resistance (OR 0.844, 95% CI 0.726-0.982), but contributed to a higher risk of MR-TB (isoniazid) (odds ratio (OR) 1.347, 95% CI 1.049-1.730; adjusted OR (aOR) 1.31, 95% CI 1.017-1.686), $P < 0.05$. In addition, overweight were positively associated with MDR-TB (OR 1.603, 95% CI 1.002-2.566; aOR 1.639, 95% CI 1.02-2.633), isoniazid + rifampicin + streptomycin resistance (OR 1.948, 95% confidence interval (CI): 1.061-3.577; aOR 2.113, 95% CI 1.141-3.912), Any isoniazid + streptomycin resistance (OR 1.472, 95% CI 1.013-2.14; aOR 1.483, 95% CI 1.017-2.164), $P < 0.05$.
CONCLUSIONS: The higher risk of MDR-TB, isoniazid + rifampicin + streptomycin resistance, Any isoniazid + streptomycin resistance, and co-morbidity among overweight population implies that routine screening for drug sensitivity and more attention on co-morbidity among overweight TB cases may be necessary. In addition, underweight TB cases have a higher risk of isoniazid resistance. Our study suggests that an in-depth study of the interaction between host metabolic activity and infection of DR-TB may contribute more to novel treatment options or preventive measures, and accelerate the implementation of the STOP TB strategy.

DOI: 10.1186/s12890-021-01774-2
PMCID: PMC8647447
PMID: 34872558

40. **Distribution patterns of drug resistance Mycobacterium tuberculosis among HIV negative and positive tuberculosis patients in Western Kenya.**

BMC Infect Dis. 2021 Nov 22;21(1):1175. doi: 10.1186/s12879-021-06887-x.

Ogwang MO(1), Imbuga M(2), Ngugi C(2), Mutharia L(3), Magoma G(2), Diero L(4).

INTRODUCTION: Globally anti-tuberculosis drug resistance is one of the major challenges affecting control and prevention of tuberculosis. Kenya is ranked among 30 high burden TB countries globally. However, there is scanty information on second line antituberculosis drug resistance among tuberculosis patients. Therefore, this study aimed at determining Mycobacterium tuberculosis drug resistant strain distribution pattern in 10 counties of Western Kenya among HIV positive and negative patients.
METHOD: A cross-sectional study was conducted in Western Kenya, which comprises 10 counties. A multistage sampling method was used where a single sub-county was randomly selected followed by sampling one high volume health facility from each

sub-county. Consenting study subjects with at least two smear positive sputum at the time of enrolment were randomly selected. The collected sputum was decontaminated with N-acetyl-L-cysteine-sodium hydroxide (NALC-NaOH) and then stained with Ziehl Neelsen Stain before visualizing the presence of bacilli under microscope at ×100 magnification with oil immersion. Further, the identified bacilli were cultured and susceptibility test carried out using known first and second line antimycobacterial tuberculosis. HIV testing was carried out using Determine® HIV-1/2 rapid test (Abbot Diagnostics, Maidenhead, United Kingdom). Those who had smear converted were dropped from the study. Finally, drug susceptibility pattern across the 10 counties of Western Kenya was evaluated.

RESULTS: Our study showed that Mycobacterium tuberculosis drug resistance among HIV negative and positive cases in Western Kenya was prevalent in all the 10 counties surveyed. Based on the drug susceptibility tests, 53.2% and 42.7% of the study samples were resistant to at least one antituberculosis drug among HIV negative and HIV positive patients respectively. The data analysis revealed that among the HIV-positive and HIV-negative patients, resistance to INH was predominant (28.5%, and 23.6%, respectively), followed by RIF (16.4% and 14.6% respectively). Second-line drug resistant strains identified among HIV negative patients included Ethionamide (0.3%), Gatifloxacin (0.3%), Amikacin (0.3%) and Capreomycin (0.3%). There was no second line drug monoresistance among HIV positive TB patients. Multi/poly drug resistance were noted among HIV-negative patients in, INH + AMK (0.7%), INH + PZA (1%), INH + GFX (0.7%, INH + ETO (0.7%, STY + ETO (1%), ETH + ETO (1.0%), INH + KAN (0.7%) and INH + CAP (0.7%) strains/cases at 95% confidence interval. Among HIV positive patients INH + GFX (1.1%), INH + ETO (0.4%) and INH + KAN (0.4%) strains of M. tuberculosis were identified with a confidence interval of 95%. Geographical distribution patterns analysis of M. tuberculosis drug polyresistant strains across the 10 counties were recorded. Among HIV TB patients, resistant strains were identified in Nyamira (INH + GFX, INH + KAN), Bungoma ((ETO + STY), Busia (ETH + ETO and STY + ETO) Homabay (RIF + AMK. ETO + ETH and ETO + STY), Kisumu (ETH + ETO and PZA + ETO) and in Kakamega, Kisii and Vihiga (INH + KAN and RIF + AMK). There was no M. tuberculosis polyresistant strain identified in Migori and Siaya counties. Among HIV positive TB patients, M. tuberculosis resistant strains were identified in three counties, Nyamira (INH + KAN) Homabay (INH + GFX and INH + AMK) and Kakamega (INH + GFX). There was no polyresistant M. tuberculosis strain identified in Migori, Bungoma, Kisii, Vihiga, Busia, Siaya and Kisumu Counties.

DISCUSSION: The distribution patterns of M. tuberculosis drug resistance among HIV negative and positive TB patients could be as a result of reported high prevalence of HIV in Western Kenya counties especially the area under study. Tuberculosis is one of the opportunistic diseases that have been shown to be the major cause of AIDS among HIV infected patients. Resent reports by National AIDS Control Council shows that Kisumu, Siaya, Homabay, Migori, Busia have the overall leading in HIV prevalence in Kenya. The low prevalence of drug resistant strains among HIV tuberculosis patients could be as a result of drug adherence

attitude adopted by HIV patients, availability of continuous counselling and close follow up and notification by healthcare workers and community health volunteers.
CONCLUSION: Drug resistant M. tuberculosis strains prevalence is still high among HIV negative and positive patients in Western Kenya with the most affected being HIV negative TB patients. It is therefore probable that the existing control measures are not adequate to control transmission of drug resistant strains. Further, miss diagnosis or delayed diagnosis of TB patients could be contributing to the emergence of M. tuberculosis drug polyresistant strains.
RECOMMENDATION: Based on the result of this study, regular TB drug resistance surveillance should be conducted to ensure targeted interventions aimed at controlling increased transmission of the tuberculosis drug resistant strains among HIV/AIDS and HIV negative patients. There is also need for improved drug resistant infection control measures, timely and rapid diagnosis and enhanced and active screening strategies of tuberculosis among suspected TB patients need to be put in place. Further, studies using a larger patient cohort and from counties across the country would shed much needed insights on the true national prevalence of different variants of M. tuberculosis drug resistance.

DOI: 10.1186/s12879-021-06887-x
PMCID: PMC8607708
PMID: 34809602 [Indexed for MEDLINE]

41. **Has the Time Come for Systematic Therapeutic Drug Monitoring of First-line and WHO Group A Anti-tuberculosis Drugs?**

Ther Drug Monit. 2021 Dec 2. doi: 10.1097/FTD.0000000000000948. Online ahead of print.

Lemaitre F(1).

Tuberculosis (TB) is a major global health issue, with approximately 10 million people being infected each year, and is the leading cause of mortality from infectious disease, with 1.5 million deaths a year. Optimal TB treatment requires a combination of drugs for an adequate treatment duration owing to persistent organisms, hardly accessible infection sites, and a high risk of resistance selection. Long-term therapy increases the risk of patients' loss of adherence, adverse drug reactions, and drug-drug interactions, potentially leading to treatment failure. The high inter-patient variability of TB drug exposure is another point eliciting interest in therapeutic drug monitoring (TDM) to optimize treatment. Studies reporting clinically relevant exposure thresholds, which might be proposed as targets toward treatment personalization, are discussed. Practical TDM strategies have also been reported to circumvent

issues related to delayed drug absorption and the need for multiple samples when evaluating the area under the curve of drug concentrations. The need for treatment individualization is further emphasized because of the development of multi-drug resistant TB, or extensively drug resistant TB. Finally, the willingness to shorten the treatment duration while maintaining success is also a driver for ensuring adequate exposure to TB drugs with TDM. The aim of the present review is to underline the role of TDM in drug-susceptible TB and World Health Organization group A TB drugs.

DOI: 10.1097/FTD.0000000000000948
PMID: 34857693

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

Thorax. 2021 Dec 7:thoraxjnl-2020-216819. doi: 10.1136/thoraxjnl-2020-216819. Online ahead of print.

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

RATIONALE: Evidence for the association between fine particulate matter (PM2.5) and mortality among patients with tuberculosis (TB) is limited. Whether greenness protects air pollution-related mortality among patients with multidrug-resistant tuberculosis (MDR-TB) is completely unknown.
METHODS: 2305 patients reported in Zhejiang and Ningxia were followed up from MDR-TB diagnosis until death, loss to follow-up or end of the study (31 December 2019), with an average follow-up of 1724 days per patient. 16-day averages of contemporaneous Normalised Difference Vegetation Index (NDVI) in the 500 m buffer of patient's residence, annual average PM2.5 and estimated oxidant capacity Ox were assigned to patients regarding their geocoded home addresses. Cox proportional hazards regression models were used to estimate HRs per 10 μg/m3 exposure to PM2.5 and all-cause mortality among the cohort and individuals across the three tertiles, adjusting for potential covariates.
RESULTS: HRs of 1.702 (95% CI 1.680 to 1.725) and 1.169 (1.162 to 1.175) were observed for PM2.5 associated with mortality for the full cohort and individuals with the greatest tertile of NDVI. Exposures to PM2.5 were stronger in association with mortality for younger patients (HR 2.434 (2.432 to 2.435)), female (2.209 (1.874 to 2.845)), patients in rural (1.780 (1.731 to 1.829)) and from Ningxia (1.221 (1.078 to 1.385)). Cumulative exposures increased the HRs of PM2.5-related mortality, while greater greenness flattened the risk with HRs reduced in 0.188-0.194 on average.

CONCLUSIONS: Individuals with MDR-TB could benefit from greenness by having attenuated associations between PM2.5 and mortality. Improving greener space and air quality may contribute to lower the risk of mortality from TB/MDR-TB and other diseases.

DOI: 10.1136/thoraxjnl-2020-216819
PMID: 34876501

43. **Sirtuin 7 Regulates Nitric Oxide Production and Apoptosis to Promote Mycobacterial Clearance in Macrophages.**

Front Immunol. 2021 Dec 3;12:779235. doi: 10.3389/fimmu.2021.779235. eCollection 2021.

Zhang S(1), Liu Y(2), Zhou X(3), Ou M(1), Xiao G(1), Li F(1), Wang Z(1), Wang Z(1), Liu L(1), Zhang G(1).

The host immune system plays a pivotal role in the containment of Mycobacterium tuberculosis (Mtb) infection, and host-directed therapy (HDT) is emerging as an effective strategy to treat tuberculosis (TB), especially drug-resistant TB. Previous studies revealed that expression of sirtuin 7 (SIRT7), a nicotinamide adenine dinucleotide (NAD+)-dependent deacetylase, was downregulated in macrophages after Mycobacterial infection. Inhibition of SIRT7 with the pan-sirtuin family inhibitor nicotinamide (NAM), or by silencing SIRT7 expression, promoted intracellular growth of Mtb and restricted the generation of nitric oxide (NO). Addition of the exogenous NO donor SNAP abrogated the increased bacterial burden in NAM-treated or SIRT7-silenced macrophages. Furthermore, SIRT7-silenced macrophages displayed a lower frequency of early apoptotic cells after Mycobacterial infection, and this could be reversed by providing exogenous NO. Overall, this study clarified a SIRT7-mediated protective mechanism against Mycobacterial infection through regulation of NO production and apoptosis. SIRT7 therefore has potential to be exploited as a novel effective target for HDT of TB.

DOI: 10.3389/fimmu.2021.779235
PMCID: PMC8678072
PMID: 34925356

44. **Tuberculosis of the spine in children - does drug resistance affect surgical**

outcomes?

Spine J. 2021 Dec;21(12):1973-1984. doi: 10.1016/j.spinee.2021.06.001. Epub 2021 Jun 8.

Pinto D(1), Dhawale A(2), Shah I(3), Rokade S(1), Shah A(1), Chaudhary K(4), Aroojis A(1), Mehta R(1), Nene A(1).

BACKGROUND CONTEXT: The emergence of drug resistance has complicated the management of spinal tuberculosis (TB). While it is well known that the medical management of drug-resistant spinal TB is more difficult, the surgical outcomes of the same have not been studied sufficiently, particularly in children.
PURPOSE: To analyze the surgical outcomes in a cohort of children treated for spinal TB, and to thus assess whether drug resistant (DR) disease is associated with poorer surgical outcomes.
STUDY DESIGN/SETTING: Retrospective observational study.
PATIENT SAMPLE: All children diagnosed and treated for tuberculous spondylodiscitis at a single center between January 2014 and June 2017.
OUTCOME MEASURES: Surgical outcomes in terms of neurological status and kyphosis angle at final follow-up, and complication rates.
METHODS: Radiographic and clinical data of children treated for spinal TB with minimum two-year follow-up were retrospectively analyzed. Data gathered included age, gender, level of spine affected, number of vertebrae involved, neurology (Frankel grade), microbiological reports, duration and type of anti-tuberculous therapy (ATT), details of Orthopaedic management and complications during treatment. In DR cases, the time from presentation to starting of second-line ATT was also assessed. Radiographs were reviewed to note the pre- and post-operative degree of kyphosis as well as the angle at final follow-up. Patients that developed major complications were compared statistically with those that did not.
RESULTS: Forty-one consecutive children (mean age 8.5 ± 4.2 years, 20 boys, 21 girls) were treated for spinal TB with a mean follow-up of 31.2 ± 6.4 months. Fifteen were managed conservatively, of which only one had DR-TB. Of the 26 managed surgically, 13 were managed with first-line ATT and 13 required second-line ATT. Of this latter group, eight had microbiologically proven drug resistance, whereas five were switched to second-line therapy presumptively because of failure to show an adequate response to first-line regimen. At last follow-up, all children had completed the prescribed course of ATT and had been declared cured. Neurological improvement was seen in all but one patient; and at last follow-up, 18 children were Frankel E, seven were Frankel D, and one was Frankel B. 1The immediate post-operative Kyphosis angle averaged 24.38° ± 15.21°. However, six children showed a subsequent worsening of kyphosis, and the Kyphosis angle at last follow-up averaged 30.96° ± 23.92°. Five children had major complications requiring revision surgery; complications included wound dehiscence, vertebral collapse, screw pull-out and implant breakage. Significantly higher number of patients in the group with complications had

required second-line ATT ($p < .05$).
CONCLUSIONS: In a cohort of children treated surgically for spinal tuberculosis, a higher complication rate, and thus poor surgical outcomes, were found to be associated with drug resistant disease.

DOI: 10.1016/j.spinee.2021.06.001
PMID: 34116216

45. **Population pharmacokinetics of bedaquiline in patients with drug-resistant TB.**

Int J Tuberc Lung Dis. 2021 Dec 1;25(12):1006-1012. doi: 10.5588/ijtld.21.0158.

Zhu H(1), Xie L(2), Liu ZQ(1), Wang B(1), Gao MQ(2), Lu Y(1).

OBJECTIVE: To develop a population pharmacokinetic (PK) model for bedaquiline (BDQ) to describe the concentration-time data from patients with multidrug-resistant TB (MDR-TB) in China.METHOD: A total of 306 PK observations from 69 patients were used in a non-linear, mixed-effects modelling (NONMEM) approach. BDQ PK can be adequately described by a three-compartment model with a transit absorption model. The impact of baseline covariates, including age, sex, height, weight, alanine aminotransferase (ALT), aspartate aminotransferase (AST), apolipoprotein (ALP), total bilirubin (TBIL), direct bilirubin (DBIL), creatinine (CR), potassium (K+), calcium (Ca++) and magnesium (Mg++) on the oral clearance (CL/F) of BDQ were investigated.RESULTS: In final population PK model, no significant covariates were found in the population PK model for BDQ. The population PK parameter estimate values for oral clearance (CL/F); CL/F between central compartment and peripheral compartment (Q1/F, Q2/F); peripheral volume of distribution (Vp1/F, VP2/F) were respectively 1.50 L/h (95% CI 1.07-1.93), 2.54 L/h (95% CI 1.67-3.41), 1,250 L (95% CI 616.9-1883.1), 2.00 L/h (95% CI 1.10-2.90) and 4,960 L (95% CI 1647.6-8272.4). Inter-individual variability on CL/F was 65.0%.CONCLUSION: This is the first study to establish a population PK model for BDQ in Chinese patients with MDR-TB. The final model adequately described the data and had good simulation characteristics. Despite some limitations, the final population PK model was stable with good accuracy of parameter estimation.

DOI: 10.5588/ijtld.21.0158
PMID: 34886931

46. **Antimycobacterial activity of acetone extract and isolated metabolites from folklore medicinal lichen Usnea laevis Nyl. against drug-sensitive and multidrug-resistant tuberculosis strains.**

J Ethnopharmacol. 2022 Jan 10;282:114641. doi: 10.1016/j.jep.2021.114641. Epub 2021 Sep 15.

Tatipamula VB(1), Annam SSP(2).

ETHNOPHARMACOLOGICAL RELEVANCE: Tuberculosis (Tb) is one of the most infectious diseases caused by Mycobacterium tuberculosis (M.t) with almost 2 million deaths yearly. Although many Tb control programs have been organised, there is an elevated number of Tb cases due to the appearance of extremely drug-resistant and multidrug-resistant (MDR) Tb strains. In the cultures of Venezuelan Andes, fruticose lichen Usnea laevis Nyl. (Usneaceae) with folklore name 'Barba de Piedra, Tusinya' is used as a natural remedy for Tb.
AIM OF THE STUDY: This study was performed to provide a scientific rationale for the folklore usage of U. laevis in treating Tb by validating its antimycobacterial activity against two drug-sensitive and four MDR-Tb strains.
MATERIALS AND METHODS: The mycobacterial inhibitory activities of acetone extract (Ul), fractions (F1-10), and isolated metabolites (1-4) of U. laevis were evaluated against M.t H37Ra using 2,3-bis-(2-methoxy-4-nitro-5-sulfophenyl)-2H-tetrazolium-5-carboxanilide reduction menadione assay (XRMA). Furthermore, Ul and 1-4 were subjected to antimycobacterial activity against M.t H37Ra, Mycobacterium smegmatis, and four MDR-Tb (MDR-A8, MDR-V791, MDR-R and MDR-40) strains using resazurin microtitre plate assay (REMA) and cytotoxicity against THP-1 macrophages using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay and their selectivity index values were also calculated.
RESULTS: Initially, Ul has shown prominent inhibitory activity (IC50 value: 5.44 ± 0.36 μg/ml) and four of its fractions (F1, F2, F5 and F7) also exhibited the best inhibitory activity (IC50 values ranged from 7.46 ± 0.19 to 71.38 ± 2.57 μg/ml) against M.t H37Ra using XRMA. Purification of these bioactive fractions identified four metabolites, namely usnic acid (1), atranorin (2), salazinic acid (3), and lobaric acid (4). From the MIC values of REMA, it was identified that Ul, 1 and 4 were more effective in inhibiting the growth of all four MDR-Tb strains, compared to first-line drug rifampicin. Interestingly, Ul has shown better antimycobacterial activity than 1-4 and rifampicin against MDR-Tb strains may be due to the synergistic effect of its metabolites. Also, the IC50 values of Ul and 1-4 on THP-1 macrophages were found to be far higher than MIC values against tested Tb strains, indicating that THP-1 macrophages were not harmfully affected at concentrations that were effective against Tb strains. Further, the calculated selectivity index values revealed the more active and non-toxicity of Ul, 1 and 4 against MDR-Tb strains than rifampicin.
CONCLUSIONS: The current study lends the first evidence for the presence of antimycobacterial metabolites in U. laevis. The results exposed the Andean folklore use of U. laevis for treating Tb, and the key biomarker metabolites were found to be 1 and 4. Hence, it can be concluded that U. laevis can be used

as a potential source for the novel drug development for MDR-Tb.

DOI: 10.1016/j.jep.2021.114641
PMID: 34536516

47. **Risk factors for mortality and multidrug resistance in pulmonary tuberculosis in Guatemala: A retrospective analysis of mandatory reporting.**

J Clin Tuberc Other Mycobact Dis. 2021 Nov 15;25:100287. doi: 10.1016/j.jctube.2021.100287. eCollection 2021 Dec.

Montes K(1), Atluri H(1), Silvestre Tuch H(2), Ramirez L(2), Paiz J(2), Hesse Lopez A(2), Bailey TC(3), Spec A(3), Mejia-Chew C(3).

BACKGROUND: Risk factors for mortality and MDR-TB in Guatemala are poorly understood. We aimed to identify risk factors to assist in targeting public health interventions.
METHODS: We performed a retrospective study of adults with pulmonary TB reported to the Guatemalan TB Program between January 1, 2016 and December 31, 2017. The primary objective was to determine risk factors for mortality in pulmonary TB. The secondary objective was to determine risk factors associated with MDR-TB.
RESULTS: Among 3,945 patients with pulmonary TB, median age was 39 years (IQR 25-54), 59% were male, 25% of indigenous ethnicity, 1.1% had MDR-TB and 3.9% died. On multivariable analysis, previous TB treatment (odds ratio [OR] 3.57, CI 2.24-5.68 [p < 0.001]), living with HIV (OR 3.98, CI 2.4-6.17 [p < 0.001]), unknown HIV diagnosis (OR 2.65, CI 1.68-4.18 [p < 0.001]), indigenous ethnicity (OR 1.79, CI 1.18-2.7 [p = 0.005]), malnutrition (OR 7.33, CI 3.24-16.59 [p < 0.001]), and lower educational attainment (OR 2.86, CI 1.43-5.88 [p = 0.003]) were associated with mortality. Prior treatment (OR 53.76, CI 25.04-115.43 [p < 0.001]), diabetes (OR 4.13, CI 2.04-8.35 [p < 0.001]), and indigenous ethnicity (OR 11.83, CI 1.46-95.73 [p = 0.02]) were associated with MDR-TB.
CONCLUSIONS: In Guatemala, both previous TB treatment and indigenous ethnicity were associated with higher TB mortality and MDR-TB risk among patients with pulmonary TB.

DOI: 10.1016/j.jctube.2021.100287
PMCID: PMC8608588
PMID: 34849409

48. **Putative extensive and pre-extensive drug resistant-tuberculosis associated with unusual genotypes on the Thailand-Myanmar border.**

Rev Inst Med Trop Sao Paulo. 2021 Dec 6;63:e85. doi: 10.1590/S1678-9946202163085. eCollection 2021.

Rudeeaneksin J(1), Klayut W(1), Srisungngam S(1), Bunchoo S(1), Toonkomdang S(2), Wongchai T(2), Chuenchom N(2), Phetsuksiri B(1)(3).

Extensive drug-resistant tuberculosis (XDR-TB) is highly life threatening and its diagnosis is usually difficult and time-consuming. Here we present the first two cases of XDR and pre-XDR-TB diagnosed in 2018 on the Thailand-Myanmar border, more specifically in Tak province. Rapid detection of XDR-TB was performed by loop-mediated isothermal amplification (LAMP), Xpert MTB/RIF, and line probe assays. Mutation analyses targeting rpoB, katG, inhA, gyrA and rrs genes showed an association with drug-resistant phenotypes, except for rifampicin resistance. Spoligotyping revealed uncommon Beijing and T2 genotypes and the analysis of M. tuberculosis interspersed repetitive unit-variable number tandem repeat (MIRU-VNTR) showed the presence of more polymorphisms. This report highlights the importance of the early detection of drug-resistant tuberculosis by molecular tests followed by phenotyping assays. Based on the up-to-date definition of XDR- and pre-XDR-TB, the susceptibility testing for bedaquiline and linezolid is required and the two reported cases may correspond to putative XDR-TB.

DOI: 10.1590/S1678-9946202163085
PMCID: PMC8660029
PMID: 34878043 [Indexed for MEDLINE]

49. **Modeling treatment effect modification in multidrug-resistant tuberculosis in an individual patientdata meta-analysis.**

Stat Methods Med Res. 2021 Dec 13:9622802211046383. doi: 10.1177/09622802211046383. Online ahead of print.

Liu Y(1), Schnitzer ME(2)(3), Wang G(1), Kennedy E(4), Viiklepp P(5), Vargas MH(6), Sotgiu G(7), Menzies D(8)(9), Benedetti A(1)(8)(10).

Effect modification occurs while the effect of the treatment is not homogeneous across the different strata of patient characteristics. When the effect of treatment may vary from individual to individual, precision medicine can be improved by identifying patient covariates to estimate the size and direction of the effect at the individual level. However, this task is statistically challenging and typically requires large amounts of data. Investigators may be interested in using the individual patient data from multiple studies to

estimate these treatment effect models. Our data arise from a systematic review of observational studies contrasting different treatments for multidrug-resistant tuberculosis, where multiple antimicrobial agents are taken concurrently to cure the infection. We propose a marginal structural model for effect modification by different patient characteristics and co-medications in a meta-analysis of observational individual patient data. We develop, evaluate, and apply a targeted maximum likelihood estimator for the doubly robust estimation of the parameters of the proposed marginal structural model in this context. In particular, we allow for differential availability of treatments across studies, measured confounding within and across studies, and random effects by study.

DOI: 10.1177/09622802211046383
PMID: 34903098

50. **A Rapid Drug Resistance Genotyping Workflow for Mycobacterium tuberculosis, Using Targeted Isothermal Amplification and Nanopore Sequencing.**

Microbiol Spectr. 2021 Nov 24;9(3):e0061021. doi: 10.1128/Spectrum.00610-21. Online ahead of print.

Gliddon HD(#)(1)(2), Frampton D(#)(3), Munsamy V(4), Heaney J(5), Pataillot-Meakin T(5), Nastouli E(5), Pym AS(4), Steyn AJC(4)(6), Pillay D(3)(4), McKendry RA(1)(7).

Phenotypic drug susceptibility testing (DST) for tuberculosis (TB) requires weeks to yield results. Although molecular tests rapidly detect drug resistance-associated mutations (DRMs), they are not scalable to cover the full genome and the many DRMs that can predict resistance. Whole-genome sequencing (WGS) methods are scalable, but if conducted directly on sputum, typically require a target enrichment step, such as nucleic acid amplification. We developed a targeted isothermal amplification-nanopore sequencing workflow for rapid prediction of drug resistance of TB isolates. We used recombinase polymerase amplification (RPA) to perform targeted isothermal amplification (37°C for 90 min) of three regions within the Mycobacterium tuberculosis genome, followed by nanopore sequencing on the MinION. We tested 29 mycobacterial genomic DNA extracts from patients with drug-resistant (DR) TB and compared our results to those of WGS by Illumina and phenotypic DST to evaluate the accuracy of prediction of resistance to rifampin and isoniazid. Amplification by RPA showed fidelity equivalent to that of high-fidelity PCR (100% concordance). Nanopore sequencing generated DRM predictions identical to those of WGS, with considerably faster sequencing run times of minutes rather than days. The sensitivity and specificity of rifampin resistance prediction for our workflow were 96.3% (95% confidence interval [CI], 81.0 to 99.9%) and 100.0% (95% CI, 15.8 to 100.0%), respectively. For isoniazid resistance prediction, the

sensitivity and specificity were 100.0% (95% CI, 86.3 to 100.0%) and 100.0% (95% CI, 39.8 to 100.0%), respectively. The workflow consumable costs per sample are less than £100. Our rapid and low-cost drug resistance genotyping workflow provides accurate prediction of rifampin and isoniazid resistance, making it appropriate for use in resource-limited settings. IMPORTANCE Current methods for diagnosing drug-resistant tuberculosis are time consuming, resulting in delays in patients receiving treatment and in transmission onwards. They also require a high level of laboratory infrastructure, which is often only available at centralized facilities, resulting in further delays to diagnosis and additional barriers to deployment in resource-limited settings. This article describes a new workflow that can diagnose drug-resistant TB in a shorter time, with less equipment, and for a lower price than current methods. The amount of TB DNA is first increased without the need for bulky and costly thermocycling equipment. The DNA is then read using a portable sequencer called a MinION, which indicates whether there are tell-tale changes in the DNA that indicate whether the TB strain is drug resistant. Our workflow could play an important role in the future in the fight against the public health challenge that is TB drug resistance.

DOI: 10.1128/Spectrum.00610-21
PMCID: PMC8612157
PMID: 34817282

51. **The experimental study of TNF-α & CRP expression in the spinal tuberculosis after instrumentation.**

Ann Med Surg (Lond). 2021 Nov 12;72:103048. doi: 10.1016/j.amsu.2021.103048. eCollection 2021 Dec.

Risantoso T(1), Hidayat M(2), Suyuti H(3), Aulann'iam(4).

INTRODUCTION: Previously, the management of spinal TB was using drugs and external stabilization. Surgical techniques were developed afterwards to clean the infected vertebral segment. The TB treatment approach is now based on immunology because the bacteria Mycobacterium tuberculosis has unique characteristics and the increasing cases of MDR (multiple drug resistant) TB due to mutation processes. TNF-α and CRP has a major role in immune activity of spinal TB. The energy from metal devices composed of ions and particles that have been used in instrumentation is expected to reduce the biomolecular and biocellular activity of the spinal tuberculosis inflammation activity. This study aims to investigate TNFα and CRP value as evaluator of bone inflammation activity in Spinal TB through experimental studies in Laboratory at Veterinary Faculty, Universitas Brawijaya.
METHODS: We investigates 40 New Zealand Rabbits which were given TB H37Rv strain infection in the vertebral body. Samples were divided into five groups namely

control rabbits, infected rabbits without intervention, infected rabbits treated by instrumentation, infected rabbits given anti-tuberculosis drugs and infected rabbits treated by instrumentation and given drugs. The cytokine levels of TNF-α and CRP were evaluated and compared as the main outcome.
RESULT: The results showed a notable TNF-α and CRP decrease in infected rabbits given drugs alone and instrumentation alone compared to infected rabbits without intervention. There was a significant TNF-α and CRP decrease in infected rabbits given drugs and treated by instrumentation compared to control rabbits and rabbits who received drugs only.
CONCLUSION: Instrumentation can reduce the inflammation activity in spinal tuberculosis by affecting the body's cytokine levels.

DOI: 10.1016/j.amsu.2021.103048
PMCID: PMC8591466
PMID: 34815862

52. **Optimising recruitment to a late-phase tuberculosis clinical trial: a qualitative study exploring patient and practitioner experiences in Uzbekistan.**

Trials. 2021 Dec 4;22(1):881. doi: 10.1186/s13063-021-05850-0.

Wharton-Smith A(1), Horter S(1), Douch E(1), Gray N(1), James N(1), Nyang'wa BT(1)(2), Singh J(3), Nusratovna PN(4), Tigay Z(5), Kazounis E(1), Allanazarova G(3), Stringer B(6).

BACKGROUND: Addressing the global burden of multidrug-resistant tuberculosis (MDR-TB) requires identification of shorter, less toxic treatment regimens. Médecins Sans Frontières (MSF) is currently conducting a phase II/III randomised controlled clinical trial, to find more effective, shorter and tolerable treatments for people with MDR-TB. Recruitment to the trial in Uzbekistan has been slower than expected; we aimed to study patient and health worker experiences of the trial, examining potential factors perceived to impede and facilitate trial recruitment, as well as general perceptions of clinical research in this context.
METHODS: We conducted a qualitative study using maximum variation, purposive sampling of participants. We carried out in-depth interviews (IDIs) and focus group discussions (FGDs) guided by semi-structured topic guides. In December 2019 and January 2020, 26 interviews were conducted with patients, Ministry of Health (MoH) and MSF staff and trial health workers, to explore challenges and barriers to patient recruitment as well as perceptions of the trial and research in general. Preliminary findings from the interviews informed three subsequent focus group discussions held with patients, nurses and counsellors. Focus groups adopted a person-centred design, brainstorming potential solutions to problems

and barriers. Interviews and FGDs were audio recorded, translated and transcribed verbatim. Thematic analysis, drawing on constant comparison, was used to analyse the data.
RESULTS: Health system contexts may compete with new approaches especially when legislative health regulations or policy around treatment is ingrained in staff beliefs, perceptions and practice, which can undermine clinical trial recruitment. Trust plays a significant role in how patients engage with the trial. Decision-making processes are dynamic and associated with relationship to diagnosis, assimilation of information, previous knowledge or experience and influence of peers and close relations.
CONCLUSIONS: This qualitative analysis highlights ways in which insights developed together with patients and healthcare workers might inform approaches towards improved recruitment into trials, with the overall objective of delivering evidence for better treatments.

DOI: 10.1186/s13063-021-05850-0
PMCID: PMC8645116
PMID: 34863253 [Indexed for MEDLINE]

53. **A Semimechanistic Model of the Bactericidal Activity of High-Dose Isoniazid against Multidrug-Resistant Tuberculosis: Results from a Randomized Clinical Trial.**

Am J Respir Crit Care Med. 2021 Dec 1;204(11):1327-1335. doi: 10.1164/rccm.202103-0534OC.

Gausi K(1), Ignatius EH(2), Sun X(3), Kim S(4), Moran L(5), Wiesner L(1), von Groote-Bidlingmaier F(6), Hafner R(7), Donahue K(8), Vanker N(6), Rosenkranz SL(3), Swindells S(9), Diacon AH(6), Nuermberger EL(2), Dooley KE(2), Denti P(1).

Rationale: There is accumulating evidence that higher-than-standard doses of isoniazid are effective against low-to-intermediate-level isoniazid-resistant strains of Mycobacterium tuberculosis, but the optimal dose remains unknown. Objectives: To characterize the association between isoniazid pharmacokinetics (standard or high dose) and early bactericidal activity against M. tuberculosis (drug sensitive and inhA mutated) and N-acetyltransferase 2 status. Methods: ACTG (AIDS Clinical Trial Group) A5312/INHindsight is a 7-day early bactericidal activity study with isoniazid at a normal dose (5 mg/kg) for patients with drug-sensitive bacteria and 5, 10, and 15 mg/kg doses for patients with inhA mutants. Participants with pulmonary tuberculosis received daily isoniazid monotherapy and collected sputum daily. Colony-forming units (cfu) on solid culture and time to positivity in liquid culture were jointly analyzed using

nonlinear mixed-effects modeling. Measurements and Main Results: Fifty-nine adults were included in this analysis. A decline in sputum cfu was described by a one-compartment model, whereas an exponential bacterial growth model was used to interpret time-to-positivity data. The model found that bacterial kill is modulated by isoniazid concentration using an effect compartment and a sigmoidal Emax relationship (a model linking the drug concentration to the observed effect). The model predicted lower potency but similar maximum kill of isoniazid against inhA-mutated compared with drug-sensitive isolates. Based on simulations from the pharmacokinetics-pharmacodynamics model, to achieve a drop in bacterial load comparable to 5 mg/kg against drug-sensitive tuberculosis, 10- and 15-mg/kg doses are necessary against inhA-mutated isolates in slow and intermediate N-acetyltransferase 2 acetylators, respectively. Fast acetylators underperformed even at 15 mg/kg. Conclusions: Dosing of isoniazid based on N-acetyltransferase 2 acetylator status may help patients attain effective exposures against inhA-mutated isolates. Clinical trial registered with www.clinicaltrials.gov (NCT01936831).

DOI: 10.1164/rccm.202103-0534OC
PMID: 34403326

54. **An updated patent review on drugs for the treatment of tuberculosis (2018-present).**

Expert Opin Ther Pat. 2021 Nov 30. doi: 10.1080/13543776.2022.2012151. Online ahead of print.

Ahmed S(1), Nandi S(1), Saxena AK(1).

INTRODUCTION: Tuberculosis (TB) caused by Mycobacterium tuberculosis (M.tb) has been a global challenge as 1.4 million deaths were reported in 2019, which included deaths attributed to HIV-TB co-infection. It is curable by the prescribed Directly Observed Treatment Short (DOTS) course, but the situation becomes critical and alarming due to multi-drug resistant (MDR) and extensively drug-resistant (XDR) tuberculosis. Hence there has been an urgent need to develop novel M.tb chemotherapeutics to overcome this situation.
AREAS COVERED: This review provides an overview and update on recent developments on the novel therapeutics for the treatment of TB from the important published and granted patents (2018-present).
EXPERT OPINION: The discovery of potent chemotherapeutics with reduced toxicity to combat M.tb particularly MDR and XDR-TB is a major challenge in antitubercular drug development. The missing of any doses during the DOTS treatment and poor immunity particularly in HIV patients has been a major cause for the development of drug resistance. Hence the major focus has to be on novel targets with their inhibitors and novel molecules both of natural and synthetic origins along with repurposed drugs for the complete eradication of

tuberculosis.

DOI: 10.1080/13543776.2022.2012151
PMID: 34846976

55. **Ethnobotanical plants used in the management of symptoms of tuberculosis in rural Uganda.**

Trop Med Health. 2021 Nov 22;49(1):92. doi: 10.1186/s41182-021-00384-2.

Oryema C(1), Rutaro K(2), Oyet SW(3), Malinga GM(3).

BACKGROUND: Tuberculosis (TB) caused by Mycobacterium tuberculosis is the 13th leading cause of death worldwide. The emergence of multidrug-resistant TB (MDR-TB) poses a major health security threat. Plants have traditionally been used as a source of medicine, since olden days and 80% of the communities in Africa still rely on herbal medicines for their healthcare. In many parts of Uganda, some plants have shown ethno-pharmacological prospects for the treatment of TB, and yet they have not been fully researched.
AIM: This study aimed to document plant species used traditionally by the herbalists and non-herbalist communities of Kitgum and Pader districts for managing symptoms of TB.
METHODS: An ethnobotanical study was carried out in 42 randomly selected villages in Kitgum and Pader districts between August 2020 and January 2021. Information was obtained by administering semi-structured questionnaires to 176 respondents identified by snowball and random sampling methods. Data were analysed and presented using descriptive statistics and Informant Consensus Factor (ICF).
RESULTS: Overall, only 27% of the respondents were knowledgeable about plants used for managing symptoms of TB. Nine plant species belonging to six families (Mimosaceae, Apiaceae, Lamiaceae, Rutaceae, Loganiaceae and Rubiaceae) were used to manage symptoms of TB. The most representative family was Rutaceae with three species, followed by Rubiaceae (two species) and the rest of the families were represented by one species each. The most frequently recorded species were Steganotaenia araliacea Hochst. (8.5%), Gardenia ternifolia Schumach. & Thonn (6.8%) and Albizia adianthifolia (Schum.) W.Wight (6.8%). Most of the medicinal plants were trees, and roots (69%) were the most frequently plant part used, followed by the bark (16%) and leaves (15%). The most common method of preparation was by pounding and mixing concoction with water. The administration of the concoctions was mostly done orally.
CONCLUSIONS: The results established the existence of few medicinal plants for managing symptoms of TB among the Acholi communities which could be used in developing new, effective plant-based antimycobacterial drugs. The few plants mentioned might face conservation threats due to exploitations of the roots. Phytochemical and toxicological studies are recommended to identify active

compounds responsible for antimycobacterial activity.

DOI: 10.1186/s41182-021-00384-2
PMCID: PMC8607616
PMID: 34809718

56. **Who Knew? Injectable TB Drugs Are Not Equal, Despite Drug Susceptibility Testing.**

Clin Infect Dis. 2021 Dec 6;73(11):e3937-e3938. doi: 10.1093/cid/ciaa617.

Hamilton CD(1).

DOI: 10.1093/cid/ciaa617
PMID: 34407174

57. **Estimating TB diagnostic costs incurred under the National Tuberculosis Elimination Programme: a costing study from Tamil Nadu, South India.**

Int Health. 2021 Dec 1;13(6):536-544. doi: 10.1093/inthealth/ihaa105.

Muniyandi M(1), Lavanya J(2), Karikalan N(1), Saravanan B(1), Senthil S(1), Selvaraju S(3), Mondal R(4).

BACKGROUND: The National Tuberculosis Elimination Programme (NTEP) of India is aiming to eliminate TB by 2025. The programme has increased its services and resources to strengthen the accurate and early detection of TB. It is important to estimate the cost of TB diagnosis in India considering the advancement and implementation of new diagnostic tools under the NTEP. The objective of this study was to estimate the unit costs of providing TB diagnostic services at different levels of public health facilities with different algorithms implemented under the NTEP in Chennai, Tamil Nadu, South India.
METHODS: This costing study was conducted from the perspective of the health system. This study used only secondary data and information that were available in the public domain. Data were collected with the approval of health authorities. The patient's diagnostic path from the point of registration until the final diagnosis was considered in the costing exercise. The unit costs of different diagnostic tools used in the NTEP implemented by Chennai Corporation were calculated.
RESULTS: We estimated the unit cost of the eight laboratory tests (Ziehl-Neelsen [ZN], fluorescence microscopy [FM], x-ray, digital x-ray, gene Xpert MTB/RIF (cartridge-based nucleic acid amplification test [NAAT] that identifies

rifampicin resistant Mycobacterium Tuberculosis) Mycobacterium Tuberculosis/Rifampicin [MTB/RIF], mycobacteria growth indicator tube [MGIT], line probe assay [LPA] and Lowenstein Jensen [LJ] culture) for diagnosis of drug-sensitive and drug-resistant TB. The unit costs included fixed and variable costs for smear examination by ZN microscopy (₹ [Indian Rupee] 326 [US${\$}$4.72], FM (₹104 [US${\$}$1.5]), x-ray (₹218 [US${\$}$3.15]), digital X-ray (₹281 [US${\$}$4.07]), gene Xpert MTB/RIF (₹1137 [US${\$}$16.47]), MGIT (₹7038 [US${\$}$102]), LPA (₹6448 [US${\$}$93.44]) and LJ culture (₹4850 [US${\$}$70.28]). Out of 10 diagnostic algorithms used for TB diagnosis, algorithms using only smear microscopy had the lowest cost, followed by smear microscopy with x-ray for drug-sensitive TB (₹104 [US${\$}$1.5] to ₹544 [US${\$}$7.88]). Diagnostic algorithms for drug-resistant TB involving LPA and gene Xpert MTB/RIF were the most expensive.
CONCLUSIONS: Understanding the various costs contributing to TB diagnosis in India provides crucial evidence for policymakers, programme managers and researchers to optimise programme spending and efficiently use resources.

DOI: 10.1093/inthealth/ihaa105
PMCID: PMC8643484
PMID: 33570132

58. **High rate of successful treatment outcomes among childhood rifampicin/multidrug-resistant tuberculosis in Pakistan: a multicentre retrospective observational analysis.**

BMC Infect Dis. 2021 Dec 4;21(1):1209. doi: 10.1186/s12879-021-06935-6.

Naz F(1), Ahmad N(2), Wahid A(1), Ahmad I(3), Khan A(1), Abubakar M(1), Khan SA(4), Khan A(5), Latif A(6), Ghafoor A(6).

BACKGROUND: There was a complete lack of information about the treatment outcomes of rifampicin/multidrug resistant (RR/MDR) childhood TB patients (age ≤ 14 years) from Pakistan, an MDR-TB 5th high burden country. Therefore, this study evaluated the socio-demographic characteristics, drug resistance pattern, treatment outcomes and factors associated with unsuccessful outcomes among childhood RR/MDR-TB patients in Pakistan.
METHODS: This was a multicentre retrospective record review of all microbiologically confirmed childhood RR/MDR-TB patients (age ≤ 14 years) enrolled for treatment at seven units of programmatic management of drug-resistant TB (PMDT) in Pakistan. The baseline and follow-up information of enrolled participants from treatment initiation until the end of treatment were retrieved from electronic nominal recording and reporting system. World Health

Organization (WHO) defined criterion was used for deciding treatment outcomes. The outcomes of "cured" and "treatment completed" were collectively grouped as successful, whereas "death", "treatment failure" and "lost to follow-up" were grouped together as unsuccessful outcomes. Multivariable binary logistic regression analysis was used to find factors associated with unsuccessful outcomes. A p-value < 0.05 reflected statistically significant findings.
RESULTS: A total of 213 children RR/MDR-TB (84 RR and 129 MDR-TB) were included in the study. Majority of them were females (74%), belonged to the age group 10-14 years (82.2%) and suffered from pulmonary TB (85.9%). A notable proportion (37.1%) of patients had no history of previous TB treatment. Patients were resistant to a median of two drugs (interquartile range: 1-4) and 23% were resistant to any second line anti-TB drug. A total of 174 (81.7%) patients achieved successful treatment outcomes with 144 (67.6%) patients being cured and 30 (14.1%) declared treatment completed. Among the 39 (18.3%) patients with unsuccessful outcomes, 35 (16.4%) died and 4 (1.9%) experienced treatment failure. In multivariable analysis, the use of ethambutol had statistically significant negative association with unsuccessful outcomes (odds ratio = 0.36, p-value = 0.02).
CONCLUSIONS: In this study, the WHO target of successful treatment outcomes (≥ 75%) among childhood RR/MDR-TB patients was achieved. The notable proportion of patients with no history of previous TB treatment (37.1%) and the disproportionately high number of female patients (74%) respectively stress for infection control measures and provision of early and high quality care for female drug susceptible TB patients.

DOI: 10.1186/s12879-021-06935-6
PMCID: PMC8642947
PMID: 34863099 [Indexed for MEDLINE]

59. **Case Report: Kanamycin Ototoxicity and MDR-TB Treatment Regimen.**

Int Med Case Rep J. 2021 Nov 26;14:815-817. doi: 10.2147/IMCRJ.S336259. eCollection 2021.

Mantefardo B(1), Sisay G(2).

INTRODUCTION: Aminoglycosides are ototoxic drugs because they have the ability to destroy the inner ear structures irreversibly. They are used to treat Gram-negative bacterial infections that are aerobic and as a second-line treatment for tuberculosis.
CASE PRESENTATION: A 40-year-old male from Dilla presented with right side chest pain and cough which is productive of whitish sputum of one-year duration, after investigation the diagnosis of multiple-drug resistant tuberculosis (MDR-TB) was

made and the patient was started with a short-term MDR-TB treatment regimen (4-6 KM-Mf-Pto-Cfz-Z-HH-E/5Mfx-Cfz-Z-E). Two and half months after the initiation of treatment, he developed decreased bilateral hearing ability and he had also vertigo, but this patient has no hearing impairment before the initiation of the anti-TB treatment. Then the diagnosis of sensor neural hearing loss secondary to drug toxicity (kanamycin) was made. Then the treatment was discontinued for four days as a result of ototoxicity and the patient was referred to Yirgalem Hospital for further workup and management.
CONCLUSION: Injectable-containing MDR-TB regimens can cause permanent hearing loss. Hearing loss during treatment for MDR-TB with kanamycin can occur at any time. Systematic monitoring of AEs during and after the end of treatment needs to be strengthened in most TB programs. It is important to monitor for hearing loss and kidney function.

DOI: 10.2147/IMCRJ.S336259
PMCID: PMC8631973
PMID: 34858067

60. **Evaluating the performance of propensity score matching based approaches in individual patient data meta-analysis.**

BMC Med Res Methodol. 2021 Nov 23;21(1):257. doi: 10.1186/s12874-021-01452-1.

Johara FT(1)(2), Benedetti A(3)(4), Platt R(3)(5), Menzies D(3)(4), Viiklepp P(6), Schaaf S(7), Chan E(8).

BACKGROUND: Individual-patient data meta-analysis (IPD-MA) is an increasingly popular approach because of its analytical benefits. IPD-MA of observational studies must overcome the problem of confounding, otherwise biased estimates of treatment effect may be obtained. One approach to reducing confounding bias could be the use of propensity score matching (PSM). IPD-MA can be considered as two-stage clustered data (patients within studies) and propensity score matching can be implemented within studies, across studies, and combining both.
METHODS: This article focuses on implementation of four PSM-based approaches for the analysis of data structure that exploit IPD-MA in two ways: (i) estimation of propensity score model using single-level or random-effects logistic regression; and (ii) matching of propensity scores (PS) across studies, within studies or preferential-within studies. We investigated the performance of these approaches through a simulation study, which considers an IPD-MA that examined the success of different treatments for multidrug-resistant tuberculosis (MDR-TB). The simulation parameters were varied according to three treatment prevalences (according to studies, 50% and 30%), three levels of heterogeneity between studies (low, moderate and high) and three levels of pooled odds ratio

(1, 1.5, 3).
RESULTS: All approaches showed greater biases at the higher levels of heterogeneity regardless of the choices of treatment prevalences. However, matching of propensity scores using within-study and preferential-within study reported better performance compared to matching across studies when treatment prevalence varied across-studies. For fixed prevalences, a random-effect propensity score model to estimate propensity scores followed by matching of propensity scores across-studies achieved lower biases compared to other PSM-based approaches.
CONCLUSIONS: Propensity score matching has wide application in health research while only limited literature is available on the implementation of PSM methods in IPD-MA, and until now methodological performance of PSM methods have not been examined. We believe, this work offers an intuition to the applied researcher for the choice of the PSM-based approaches.

DOI: 10.1186/s12874-021-01452-1
PMCID: PMC8609730
PMID: 34814845

61. **Clinical characteristic, Common sites and Drug resistance profile in Culture-confirmed EPTB/ HIV co-infection patients, Southwest of China.**

J Glob Antimicrob Resist. 2021 Dec 14:S2213-7165(21)00272-1. doi: 10.1016/j.jgar.2021.10.028. Online ahead of print.

Wang DM(1), Li QF(2), Zhu M(3), Xu YH(4), Liao Y(5).

OBJECTIVES: There are few reports on EPTB/HIV co-infection patients, especially the drug resistance profile of culture-confirmed EPTB. The purpose of our study was to analysis the clinical characteristic, common sites and drug resistance profile of culture-confirmed EPTB/HIV co-infection patients in recent years in southwest of China.
METHODS: A total of 201 EPTB/HIV co-infection cases were selected for this study. Patient demographic and clinical characteristics were collected. Mycobacterium tuberculosis drug sensitivity testing was performed using the microporousplate ratio method.
RESULTS: For the 2884 culture-confirmed EPTB cases recruited, patients were predominantly male1921/2884(66.6%). Mean age was 31years. Two hundred and one cases were EPTB/ HIV co-infection patients(7.0 %), from 201 cases male make up 84.6% (170/201), mean age was 42 years (range 13-86/year). During the 7-years period, the mean number of EPTB/ HIV co-infection cases was 29 per year(range 12-49/year) at this institution. Diarrhea, headache and fever were the most common presenting symptom.DST results showed the resistance to any

anti-tuberculosis drug was observed in 62(30.8%) patient isolates, while multidrug-resistant TB and extensively drug-resistant TB were found in 14(7.0%) and 10(5.0%) patients, respectively. The distribution of EPTB tissue type mainly in Meningeal and Lymph node, varies between different genders.
CONCLUSIONS: The immune level of EPTB/HIV co-infected patients was low and most were in advanced AIDS stage. Mainly young male, and the site of EPTB was mainly in the Meningeal and Lymph node. The most common symptoms were diarrhea, headache and fever and high rates of drug resistance were found.

DOI: 10.1016/j.jgar.2021.10.028
PMID: 34920176

62. **Single ascending dose safety, tolerability and pharmacokinetic study of econazole in healthy volunteers.**

Expert Rev Anti Infect Ther. 2021 Dec 16. doi: 10.1080/14787210.2022.2016392. Online ahead of print.

Khera H(1), Pandey AK(1), Shafiq N(1), Khuller GK(2), Kondel R(1), Panditrao BA(1), Gamad N(1), Rohilla R(1), Bhattacharjee S(1), Murali N(1), Cvn H(1), Belavagi D(1), Mothsara C(1), Singh M(3), Sharma N(4), Behera D(5), Malhotra S(1).

INTRODUCTION: : Econazole has been found efficacious as antitubercular in in vitro and in vivo animal studies. However, only limited information is available for its safety and pharmacokinetics in humans. In our present study we have conducted single ascending dose, safety & pharmacokinetic evaluation in healthy human volunteers with the purpose of enabling transalation for tuberculosis.
METHODS: : This study was conducted as a single-centre, ascending-dose, placebo-controlled, double blind design. Three ascending dose were chosen (250mg, 500mg and 1000mg) to be administered as a single oral dose. The volunteers were screened for potential eligibility. Participants were randomized to receive either Econazole or Placebo in a 6:2 design. Safety assessments and pharmacokinetic evaluations were carried out for each cohort.
RESULTS: Econazole was found to be safe at all dose levels. No serious or severe adverse events occurred during the study. The AUC(0-∞) showed a response relationship with a value of 49 ± 3.47 hr* µg/ml, 17. 86 ± 8.40 hr* µg/ml, 35.54 ± 13.94 hr* µg/ml for 250mg, 500mg and 1000mg respectively.
CONCLUSION: Based on the findings of our study, a dose of 500mg Econazole, once a day orally was considered as appropriate for further evaluation.

DOI: 10.1080/14787210.2022.2016392
PMID: 34913825

63. **Whole-Genome Sequencing to Identify Missed Rifampicin and Isoniazid Resistance Among Tuberculosis Isolates-Chennai, India, 2013-2016.**

Front Microbiol. 2021 Nov 22;12:720436. doi: 10.3389/fmicb.2021.720436. eCollection 2021.

Tamilzhalagan S(1), Shanmugam S(1), Selvaraj A(1), Suba S(1), Suganthi C(1), Moonan PK(2), Surie D(2), Sathyanarayanan MK(1), Gomathi NS(1), Jayabal L(3), Sachdeva KS(4), Selvaraju S(1), Swaminathan S(1)(5), Tripathy SP(1), Hall PJ(2), Ranganathan UD(1).

India has a high burden of drug-resistant tuberculosis (DR TB) and many cases go undetected by current drug susceptibility tests (DSTs). This study was conducted to identify rifampicin (RIF) and isoniazid (INH) resistance associated genetic mutations undetected by current clinical diagnostics amongst persons with DR TB in Chennai, India. Retrospectively stored 166 DR TB isolates during 2013-2016 were retrieved and cultured in Löwenstein-Jensen medium. Whole genome sequencing (WGS) and MGIT DST for RIF and INH were performed. Discordant genotypic and phenotypic sensitivity results were repeated for confirmation and the discrepant results considered final. Further, drug resistance-conferring mutations identified through WGS were analyzed for their presence as targets in current WHO-recommended molecular diagnostics. WGS detected additional mutations for rifampicin and isoniazid resistance than WHO-endorsed line probe assays. For RIF, WGS was able to identify an additional 10% (15/146) of rpoB mutant isolates associated with borderline rifampicin resistance compared to MGIT DST. WGS could detect additional DR TB cases than commercially available and WHO-endorsed molecular DST tests. WGS results reiterate the importance of the recent WHO revised critical concentrations of current MGIT DST to detect low-level resistance to rifampicin. WGS may help inform effective treatment selection for persons at risk of, or diagnosed with, DR TB.

DOI: 10.3389/fmicb.2021.720436
PMCID: PMC8645853
PMID: 34880835

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

Ocul Immunol Inflamm. 2021 Dec 17:1-10. doi: 10.1080/09273948.2021.2002367.

Online ahead of print.

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

PURPOSE: To report pre and post treatment levels of VEGF-A in the aqueous humour of patients with intraocular tubercular granulomas and study the effect of a combined intravitreal anti-VEGF bevacizumab and moxifloxacin therapy on their regression.
METHODS: Aqueous samples of 10 consecutive patients with intraocular tubercular granulomas obtained before and after initiating treatment were subjected to ELISA for analysing intraocular VEGF-A levels. Intravitreal injections of bevacizumab and moxifloxacin were given weekly till complete regression of these granulomas. All patients received the usual four-drug ATT and oral corticosteroids.
RESULTS: Mean baseline VEGF-A level was 1004.27±411.40 pg/ml (401.32-1688.95) that reduced significantly to 27.62±46.86 pg/ml (6.9-131.83) at the last injection. Meannumber of intravitreal injections was 3.1 (2-4). We found significant correlation of decreasing levels of aqueous VEGF-A with the clinical regression of these tubercular granulomas.
CONCLUSIONS: Intraocular TB granulomas have high levels of VEGF-A. Weekly intravitreal injections of anti-VEGF bevacizumab with moxifloxacin as an adjunct to the standard care may cause prompt regression of tubercular granulomas.Abbreviations: TB: Tuberculosis; IOTB: Intraocular tuberculosis; VEGF: Vascular endothelial growth factor; RD: Retinal detachment; Mtb: Mycobacterium tuberculosis; ATT: Antitubercular therapy; AMD: Age-related macular degeneration; SRF: Subretinal fluid; ELISA: Enzyme immunosorbent assay; PCR: Polymerase chain reaction; ONH: Optic nerve head; MDR-TB: Multidrug-resistant tuberculosis; pg/ml: picogram/milliliter; ESR: Erythrocyte sedimentation rate; CECT: Contrast enhanced computed tomography; DNA: Deoxyribonucleic acid; RNA: Ribonucleic acid; BSL: Biosafety level; BCVA: Best corrected visual acuity; HM: Hand movements; KP: Keratic precipitates; PSC: Posterior subcapsular cataract; PS: Posterior synechiae; CRA: Chorio-retinal atrophy; IVMP: Intravenous methyl prednisolone; OCT: Optical coherence tomography; RPE: Retinal pigment epithelium; FFA: Fundus fluorescein angiography; ICG: Indocyanine angiography; RAP: Retinal arterial proliferans.

DOI: 10.1080/09273948.2021.2002367
PMID: 34919497

65. **Strong Increase in Moxifloxacin Resistance Rate among Multidrug-Resistant Mycobacterium tuberculosis Isolates in China, 2007 to 2013.**

Microbiol Spectr. 2021 Dec 1;9(3):e0040921. doi: 10.1128/Spectrum.00409-21.
Online ahead of print.

Xia H(1), Zheng Y(1), Liu D(2), Wang S(1), He W(1), Zhao B(1), Song Y(1), Ou X(1), Zhou Y(1), van den Hof S(3), Cobelens F(4), Zhao Y(1).

We designed this study to determine the trend of moxifloxacin resistance among multidrug-resistant tuberculosis (MDR-TB) patients from 2007 to 2013 in China to inform the composition of multidrug-resistant/rifampicin-resistant tuberculosis (MDR/RR-TB) treatment regimens. We assessed moxifloxacin resistance among MDR-TB isolates collected in national drug resistance surveys in 2007 and 2013 that included 3,634 smear-positive and 7,206 culture-positive pulmonary tuberculosis patients, respectively. Moxifloxacin susceptibility was examined by a Mycobacterium growth indicator tube (MGIT) 960 for the 2007 isolates, and by the minimum inhibitory concentration (MIC) method for the 2013 isolates, at both breakpoints 0.5 and 2.0 μg/mL. Risk factors were explored through multivariable log-binominal regression analysis. Mutations in gyrA and gyrB for part of the isolates were also studied through sequencing. Of 401 MDR strains isolated in 2007, moxifiloxacin resistance could be determined for 319 (79.6%): 41 (12.9%) and 10 (3.1%) were resistant at 0.5 and 2.0 μg/mL, respectively. Of 365 MDR strains isolated in 2013, 338 (92.6%) could be analyzed: 140 (41.4%) and 79 (23.4%) were resistant at 0.5 and 2.0 μg/mL. For patients in 2007, no characteristics were significantly associated with moxifloxacin resistance. For patients in 2013, patients aged ≥60 years (adjusted prevalence ratio [aPR], 1.46; 95% confidence interval [CI], 1.10 to 1.93) were more likely to have resistance at 0.5 μg/mL, whereas those residing in eastern China compared to those in central China had an increased risk of resistance at both 0.5 (aPR, 1.85; 95% CI, 1.38 to 2.48) and 2.0 μg/mL (aPR, 2.14; 95% CI, 1.35 to 3.40). Sequencing results were obtained for 245 and 266 MDR-TB isolates in 2007 and 2013, respectively. In total, 34 of 38 (89.5%) and 89 of 104 (85.6%) of 2007 and 2013 moxifloxacin-resistant (0.5 μg/mL) MDR-TB strains had mutations in the gyrA and gyrB gene, respectively. Asp94Gly was the most common mutation among 2007 (11 of 38, 28.9%) and 2013 isolates (24 of 104, 23.1%) and conferred high-level moxifloxacin resistance. Moxifloxacin resistance among MDR-TB patients in China increased from modest to high from 2007 to 2013. Moxifloxacin should be used carefully as a potentially effective drug for composing MDR/RR-TB regimens especially for elderly patients in China. Individual susceptibility testing especially rapid molecular-based assays should be conducted to confirm the susceptibility to moxifloxacin. IMPORTANCE China is one of the high-burden countries for multidrug-resistant/rifampicin-resistant tuberculosis (MDR/RR-TB). Moxifloxacin is one of the critical antituberculosis drugs for MDR/RR-TB treatment. Susceptibility to moxifloxacin is therefore very important to compose effective regimens and to provide protection against development of resistance of companion drugs such as bedaquiline and linezolid. There are, however, no nationally representative data on moxifloxacin resistance among MDR/RR-TB cases in China. Therefore, we assessed the resistance prevalence for moxifloxacin among MDR-TB strains isolated in national drug resistance surveys in 2007 and 2013 that covered 72 sites around the country. We demonstrate that the prevalence of moxifloxacin resistance in MDR-TB isolates increased from modest

to high, which should prompt the national tuberculosis program to use moxifloxacin cautiously in second-line regimens to treat MDR/RR-TB unless susceptibility can be laboratory-confirmed.

DOI: 10.1128/Spectrum.00409-21
PMCID: PMC8635133
PMID: 34851179

66. **Heterogeneous fitness landscape cues, pknG low expression, and phthiocerol dimycocerosate low production of Mycobacterium tuberculosis ATCC25618 rpoB S450L in enriched broth.**

Tuberculosis (Edinb). 2021 Dec 3;132:102156. doi: 10.1016/j.tube.2021.102156. Online ahead of print.

Rodríguez-Beltrán É(1), López GD(2), Anzola JM(3), Rodríguez-Castillo JG(1), Carazzone C(2), Murcia MI(4).

Multidrug-resistant tuberculosis (isoniazid/rifampin[RIF]-resistant TB) ravages developing countries. Fitness is critical in clinical outcomes. Previous studies on RIF-resistant TB (RR-TB) showed competitive fitness gains and losses, with rpoB-S450L as the most isolated/fit mutation. This study measured virulence/resistance genes, phthiocerol dimycocerosate (PDIM) levels and their relationship with rpoB S450L ATCC25618 RR-TB strain fitness. After obtaining 10 different RR-TB GenoType MTBDRplus 2.0-genotyped isolates (with nontyped, S441, H445 and S450 positions), only one S450L isolate (R9, rpoB-S450L ATCC 25618, RR 1 μg/mL) was observed, with H445Y being the most common. A competitive fitness in vitro assay with wild-type (wt) ATCC 25618: R9 1:1 in 50 mL Middlebrook 7H9/OADC was performed, and generation time (G) in vitro and relative fitness were obtained. mRNA and PDIM were extracted on log and stationary phases. Fitness decreased in rpoB S450L and H445Y strains, with heterogeneous fitness cues in three biological replicas of rpoB-S450L: one high and two low fitness replicas. S450L strain had significant pknG increase. Compared with S450L, wt-rpoB showed increased polyketide synthase ppsA expression and high PDIM peak measured by HPLC-MS in log phase compared to S450L. This contrasts with previously increased PDIM in other RR-TB isolates.

DOI: 10.1016/j.tube.2021.102156
PMID: 34891037

67. **Exploring disordered loops in DprE1 provides a functional site to combat drug-resistance in Mycobacterium strains.**

Eur J Med Chem. 2022 Jan 5;227:113932. doi: 10.1016/j.ejmech.2021.113932. Epub 2021 Oct 20.

Liu J(1), Dai H(2), Wang B(3), Liu H(4), Tian Z(5), Zhang Y(6).

As an anti-tuberculosis target, DprE1 contains two flexible loops (Loop I and Loop II) which have never been exploited for developing DprE1 inhibitors. Here Leu317 in Loop II was discovered as a new functional site to combat drug-resistance in Mycobacterium strains. Based on TCA1, LZDT1 was designed to optimize the hydrophobic interaction with Leu317. A subsequent biochemical and cellular assay displayed increased potency of LZDT1 in inhibiting DprE1 and killing drug-sensitive/-resistant Mycobacterium strains. The improved activity of LZDT1 and its analogue LZDT2 against multidrug resistant tuberculosis was particularly highlighted. For LZDT1, its enhanced interaction with Leu317 also impaired the drug-insensitivity of DprE1 caused by Cys387 mutation. A new nonbenzothiazole lead (LZDT10) with reduced Cys387-dependence was further produced by optimizing interactions with Leu317, improvement directions for LZDT10 were discussed as well. Our research underscores the value of potential functional sites in disordered loops, and affords a feasible way to develop these functional sites into opportunities for drug-resistance management.

DOI: 10.1016/j.ejmech.2021.113932
PMID: 34700267

68. **A novel ensemble based recommendation approach using network based analysis for identification of effective drugs for Tuberculosis.**

Math Biosci Eng. 2022 Jan;19(1):873-891. doi: 10.3934/mbe.2022040. Epub 2021 Nov 22.

Haldar R(1), Narayanan SJ(1).

Tuberculosis (TB) is a fatal infectious disease which affected millions of people worldwide for many decades and now with mutating drug resistant strains, it poses bigger challenges in treatment of the patients. Computational techniques might play a crucial role in rapidly developing new or modified anti-tuberculosis drugs which can tackle these mutating strains of TB. This research work applied a computational approach to generate a unique recommendation list of possible TB drugs as an alternate to a popular drug, EMB, by first securing an initial list of drugs from a popular online database, PubChem, and thereafter applying an ensemble of ranking mechanisms. As a novelty, both the pharmacokinetic properties and some network based attributes

of the chemical structure of the drugs are considered for generating separate recommendation lists. The work also provides customized modifications on a popular and traditional ensemble ranking technique to cater to the specific dataset and requirements. The final recommendation list provides established chemical structures along with their ranks, which could be used as alternatives to EMB. It is believed that the incorporation of both pharmacokinetic and network based properties in the ensemble ranking process added to the effectiveness and relevance of the final recommendation.

DOI: 10.3934/mbe.2022040
PMID: 34903017

69. **Incidence and predictors of mortality among persons receiving second-line tuberculosis treatment in sub-Saharan Africa: A meta-analysis of 43 cohort studies.**

PLoS One. 2021 Dec 10;16(12):e0261149. doi: 10.1371/journal.pone.0261149. eCollection 2021.

Edessa D(1), Adem F(1), Hagos B(2), Sisay M(3).

BACKGROUND: Drug resistance remains from among the most feared public health threats that commonly challenges tuberculosis treatment success. Since 2010, there have been rapid evolution and advances to second-line anti-tuberculosis treatments (SLD). However, evidence on impacts of these advances on incidence of mortality are scarce and conflicting. Estimating the number of people died from any cause during the follow-up period of SLD as the incidence proportion of all-cause mortality is the most informative way of appraising the drug-resistant tuberculosis treatment outcome. We thus aimed to estimate the pooled incidence of mortality and its predictors among persons receiving the SLD in sub-Saharan Africa.
METHODS: We systematically identified relevant studies published between January, 2010 and March, 2020, by searching PubMed/MEDLINE, EMBASE, SCOPUS, Cochrane library, Google scholar, and Health Technology Assessment. Eligible English-language publications reported on death and/or its predictors among persons receiving SLD, but those publications that reported death among persons treated for extensively drug-resistant tuberculosis were excluded. Study features, patients' clinical characteristics, and incidence and/or predictors of mortality were extracted and pooled for effect sizes employing a random-effects model. The pooled incidence of mortality was estimated as percentage rate while risks of the individual predictors were appraised based on their independent associations with the mortality outcome.
RESULTS: A total of 43 studies were reviewed that revealed 31,525 patients and 4,976 deaths. The pooled incidence of mortality was 17% (95% CI: 15%-18%; I2 = 91.40; P = 0.00). The studies used varied models in identifying predictors of

mortality. They found diagnoses of clinical conditions (RR: 2.36; 95% CI: 1.82-3.05); excessive substance use (RR: 2.56; 95% CI: 1.78-3.67); HIV and other comorbidities (RR: 1.96; 95% CI: 1.65-2.32); resistance to SLD (RR: 1.75; 95% CI: 1.37-2.23); and male sex (RR: 1.82; 95% CI: 1.35-2.44) as consistent predictors of the mortality. Few individual studies also reported an increased incidence of mortality among persons initiated with the SLD after a month delay (RR: 1.59; 95% CI: 0.98-2.60) and those persons with history of tuberculosis (RR: 1.21; 95% CI: 1.12-1.32).
CONCLUSIONS: We found about one in six persons who received SLD in sub-Saharan Africa had died in the last decade. This incidence of mortality among the drug-resistant tuberculosis patients in the sub-Saharan Africa mirrors the global average. Nevertheless, it was considerably high among the patients who had comorbidities; who were diagnosed with other clinical conditions; who had resistance to SLD; who were males and substance users. Therefore, modified measures involving shorter SLD regimens fortified with newer or repurposed drugs, differentiated care approaches, and support of substance use rehabilitation programs can help improve the treatment outcome of persons with the drug-resistant tuberculosis.
TRIAL REGISTRATION NUMBER: CRD42020160473; PROSPERO.

DOI: 10.1371/journal.pone.0261149
PMCID: PMC8664218
PMID: 34890421

70. **IMB-XMA0038, a new inhibitor targeting aspartate-semialdehyde dehydrogenase of Mycobacterium tuberculosis.**

Emerg Microbes Infect. 2021 Dec;10(1):2291-2299. doi: 10.1080/22221751.2021.2006578.

Wang X(1), Yang R(2), Liu S(1), Guan Y(1), Xiao C(1), Li C(2), Meng J(1), Pang Y(2), Liu Y(1).

The emergence of drug-resistant tuberculosis (TB) constitutes a major challenge to TB control programmes. There is an urgent need to develop effective anti-TB drugs with novel mechanisms of action. Aspartate-semialdehyde dehydrogenase (ASADH) is the second enzyme in the aspartate metabolic pathway. The absence of the pathway in humans and the absolute requirement of aspartate in bacteria make ASADH a highly attractive drug target. In this study, we used ASADH coupled with Escherichia coli type III aspartate kinase (LysC) to establish a high-throughput screening method to find new anti-TB inhibitors. IMB-XMA0038 was identified as an inhibitor of MtASADH with an IC50 value of 0.59 μg/mL through screening. The interaction between IMB-XMA0038 and MtASADH was confirmed by surface plasmon resonance (SPR) assay and molecular docking analysis. Furthermore, IMB-XMA0038 was found to inhibit various drug-resistant MTB strains potently with minimal

inhibitory concentrations (MICs) of 0.25-0.5 μg/mL. The conditional mutant strain MTB::asadh cultured with different concentrations of inducer (10-5 or 10-1 μg/mL pristinamycin) resulted in a maximal 16 times difference in MICs. At the same time, IMB-XMA0038 showed low cytotoxicity in vitro and vivo. In mouse model, it encouragingly declined the MTB colony forming units (CFU) in lung by 1.67 log10 dosed at 25 mg/kg for 15 days. In conclusion, our data demonstrate that IMB-XMA0038 is a promising lead compound against drug-resistant tuberculosis.

DOI: 10.1080/22221751.2021.2006578
PMCID: PMC8648042
PMID: 34779708

71. **Introduction of new drugs for drug-resistant TB in Iraq.**

Int J Tuberc Lung Dis. 2021 Dec 1;25(12):1041-1042. doi: 10.5588/ijtld.21.0356.

Tesfahun H(1), Moussally K(2), Al-Ani NA(3), Al-Salhi LG(3), Kyi HA(1), Simons S(4), Isaakidis P(5), Ferlazzo G(5), Pangtey HK(1), Mankhi AA(3).

DOI: 10.5588/ijtld.21.0356
PMID: 34886937

72. **Antimycobacterial compound of chitosan and ethambutol: ultrastructural biological evaluation in vitro against Mycobacterium tuberculosis.**

Appl Microbiol Biotechnol. 2021 Dec;105(24):9167-9179. doi: 10.1007/s00253-021-11690-4. Epub 2021 Nov 29.

Oliveira MEFAG(1), Silva YJA(2), Azevedo LA(2), Linhares LA(3), Montenegro LML(3), Alves S Jr(4), Amorim RVS(5).

Chitosan (CS) is a promising biopolymer and has been tested as a complement to the action and compensation of toxicity presented by anti-tuberculosis drugs. The present work studied the adjuvant effect of CS with the drug ethambutol (EMB) as a compound (CS-EMB), to explore its antimicrobial and cytotoxic activity, using transmission electron microscopy (TEM), to examine ultracellular changes that represent possible antimycobacterial action of CS on Mycobacterium tuberculosis (Mtb). Antimycobacterial activities were tested against reference strains Mtb ATCC® H37Rv and multidrug resistant (MDR). In vitro cytotoxicity tests were performed on Raw 264.7. For the studied compounds, morphological, ultrastructural, and physical-chemical analyses were performed. Drug-polymer interactions that occur through the H bridges were confirmed by physical-chemical analyses. The CS-EMB compound is stable at pHs of 6.5-7.5,

allowing its release at physiological pH. The antibacterial activity (minimum inhibitory concentration) of the CS-EMB compound was 50% greater than that of the EMB in the H37Rv and MDR strains and the ultrastructural changes in the bacilli observed by TEM proved that the CS-EMB compound has a bactericidal action, allowing it to break down the Mtb cell wall. The cytotoxicity of CS-EMB was higher than that of isolated EMB, IC50 279, and 176 μg/mL, respectively. It is concluded that CS-EMB forms a promising composite against strains Mtb H37Rv and multidrug resistant (MDR-TB).Key points• Our study will be the first to observe ultrastructurally the effects of the CS-EMB compound on Mtb cells.• CS-EMB antimicrobial activity in a multidrug-resistant clinical strain.• The CS-EMB compound has promising potential for the development of a new drug to fight tuberculosis.

DOI: 10.1007/s00253-021-11690-4
PMID: 34841463 [Indexed for MEDLINE]

73. **Operational Research to Inform Programmatic Approaches to the Management of Tuberculosis in Uzbekistan.**

Int J Environ Res Public Health. 2021 Nov 23;18(23):12308. doi: 10.3390/ijerph182312308.

Gadoev J(1), Harries AD(2)(3), Korotych O(4), Kumar AMV(2)(5)(6), Dadu A(4), Kuppens L(1), Parpieva N(7), Abdusamatova B(8), Yedilbayev A(4), Dara M(4).

Globally, an estimated 10 million people fell ill with tuberculosis (TB) in 2019, a number that has been declining very slowly in recent years [...].

DOI: 10.3390/ijerph182312308
PMCID: PMC8656530
PMID: 34886030

74. **Re: Multidrug-resistant tuberculosis during pregnancy and adverse birth outcomes: a systematic review and meta-analysis: Practice-embedded research to address knowledge gaps in multidrug-resistant tuberculosis in pregnancy.**

BJOG. 2021 Dec;128(13):2209-2210. doi: 10.1111/1471-0528.16873. Epub 2021 Sep 7.

Jana N(1), Arora N(2), Tripathi SK(3).

DOI: 10.1111/1471-0528.16873

PMID: 34490969 [Indexed for MEDLINE]

75. **Authors' reply re: Multidrug-resistant tuberculosis during pregnancy and adverse birth outcomes: a systematic review and meta-analysis: Practice-embedded research to address knowledge gaps in multidrug-resistant tuberculosis in pregnancy.**

BJOG. 2021 Dec;128(13):2210-2211. doi: 10.1111/1471-0528.16872. Epub 2021 Sep 15.

Alene KA(1)(2), Jegnie A(3), Adane AA(2)(4).

DOI: 10.1111/1471-0528.16872
PMID: 34524715 [Indexed for MEDLINE]

76. **Sterile tuberculous granuloma in a patient with XDR-TB treated with bedaquiline, pretomanid and linezolid.**

BMJ Case Rep. 2021 Dec 7;14(12):e245612. doi: 10.1136/bcr-2021-245612.

Howell P(1), Upton C(2), Mvuna N(3), Olugbosi M(4).

Drug-resistant tuberculosis (DR-TB) continues to pose a threat to the global eradication of TB. Regimens for extensively drug-resistant (XDR) TB are lengthy and poorly tolerated, often with unsuccessful outcomes. The TB Alliance Nix-TB trial investigated the safety and efficacy of a 26-week regimen of bedaquiline, pretomanid and linezolid (BPaL) in participants with XDR-TB, multidrug-resistant (MDR) TB treatment failure or intolerance. In this trial 9 out of 10 participants were cured. We describe a trial participant with XDR-TB who presented with new-onset seizures soon after BPaL treatment completion. Imaging showed a right temporal ring-enhancing lesion, and a sterile tuberculous granuloma was confirmed after a diagnostic, excisional biopsy. Learning points include management of a participant with a tuberculoma after BPaL completion, efficacy of new medications for central nervous system (CNS) TB and a review of their CNS penetration. This is the first case of pretomanid use in CNS TB.

DOI: 10.1136/bcr-2021-245612
PMID: 34876446 [Indexed for MEDLINE]

77. **Factors Associated with Unfavourable Treatment Outcomes in Patients with**

Tuberculosis: A 16-Year Cohort Study (2005-2020), Republic of Karakalpakstan, Uzbekistan.

Int J Environ Res Public Health. 2021 Dec 5;18(23):12827. doi: 10.3390/ijerph182312827.

Gadoev J(1), Asadov D(2), Harries AD(3)(4), Kumar AMV(3)(5)(6), Boeree MJ(7), Hovhannesyan A(8), Kuppens L(1), Yedilbayev A(8), Korotych O(8), Hamraev A(2), Kudaybergenov K(9), Abdusamatova B(10), Khudanov B(10), Dara M(8).

Tuberculosis (TB) remains a public health burden in the Republic of Karakalpakstan, Uzbekistan. This region-wide retrospective cohort study reports the treatment outcomes of patients registered in the TB electronic register and treated with first-line drugs in the TB Programme of the Republic of Karakalpakstan from 2005-2020 and factors associated with unfavourable outcomes. Among 35,122 registered patients, 24,394 (69%) patients were adults, 2339 (7%) were children, 18,032 (51%) were male and 19,774 (68%) lived in rural areas. Of these patients, 29,130 (83%) had pulmonary TB and 7497 (>22%) had been previously treated. There were 7440 (21%) patients who had unfavourable treatment outcomes. Factors associated with unfavourable treatment outcomes included: increasing age, living in certain parts of the republic, disability, pensioner status, unemployment, being HIV-positive, having pulmonary TB, and receiving category II treatment. Factors associated with death included: being adult and elderly, living in certain parts of the republic, having a disability, pensioner status, being HIV-positive, and receiving category II treatment. Factors associated with failure included: being adolescent, female, having pulmonary TB. Factors associated with loss to follow-up included: being male, disability, pensioner status, unemployment, receiving category II treatment. In summary, there are sub-groups of patients who need special attention in order to decrease unfavourable treatment outcomes.

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PMCID: PMC8657882
PMID: 34886554 [Indexed for MEDLINE]

78. **Assessing the utility of the Xpert Mycobacterium tuberculosis/rifampin assay for analysis of bronchoalveolar lavage fluid in patients with suspected pulmonary tuberculosis.**

J Clin Lab Anal. 2021 Dec 1:e24154. doi: 10.1002/jcla.24154. Online ahead of print.

Bai W(1), Liu L(2), Wu L(1), Chen S(3), Wu S(1), Wang Z(4), Xu K(1), Chi Q(5), Pan Y(6), Xu X(6).

BACKGROUND: There is limited research assessing the utility of the Xpert Mycobacterium tuberculosis/rifampin (MTB/RIF) assay for the analysis of bronchoalveolar lavage fluid (BALF) in Chinese patients with suspected pulmonary tuberculosis (PTB). Thus, our objective was to determine the diagnostic accuracy of the Xpert MTB/RIF assay and evaluate its utility for the determination of rifampicin resistance.
METHODS: We retrospectively analyzed BALF from 214 patients with suspected PTB between January 2018 and March 2019. Using mycobacterial culture or final clinical diagnosis as the reference standard, the diagnostic accuracy of the smear microscopy (SM), tuberculosis bacillus DNA (TB-DNA), Xpert MTB/RIF assay, and the determination of rifampicin resistance based on the Xpert MTB/RIF assay were compared.
RESULTS: As compared to mycobacterial culture, the sensitivity of the Xpert MTB/RIF assay, SM, and TB-DNA were 85.5% (74.2%-93.1%), 38.7% (26.6%-51.9%), and 67.7% (54.7%-79.1%), respectively. As compared to the final diagnosis, the specificity of the Xpert MTB/RIF assay, SM, and TB-DNA were 100.0% (95.9%-100.0%), 94.3% (87.1%-98.1%), and 98.9% (93.8%-100.0%), respectively. The sensitivity and specificity of the rifampicin resistance detection using the Xpert MTB/RIF assay were 100% and 98.0%, respectively, with liquid culture as the reference.
CONCLUSIONS: This study demonstrates that the analysis of BALF with the Xpert MTB/RIF assay provides a rapid and accurate tool for the early diagnosis of PTB. The accuracy of diagnosis was superior compared with the SM and TB-DNA. Moreover, Xpert is a quick and accurate method for the diagnosis of rifampicin-resistant tuberculosis and can also provide more effective guidance for the treatment of PTB or multidrug-resistant tuberculosis (MDR-TB).

DOI: 10.1002/jcla.24154
PMID: 34850984

79. **Images in Vascular Medicine: Multiple Rasmussen aneurysms in noncavitary, multidrug-resistant tuberculosis.**

Vasc Med. 2021 Nov 22:1358863X211056681. doi: 10.1177/1358863X211056681. Online ahead of print.

Cueto-Robledo G(1)(2)(3), Graniel-Palafox LE(4), Garcia-Cesar M(2), Cueto-Romero HD(1), Roldan-Valadez E(5)(6).

DOI: 10.1177/1358863X211056681
PMID: 34802310

80. **Expanding the TB Cascade of Care to Treat Undiagnosed and Subclinical TB in High Burden Settings.**

Am J Respir Crit Care Med. 2021 Nov 24. doi: 10.1164/rccm.202111-2528ED. Online ahead of print.

O'Donnell M(1), Mathema B(2).

DOI: 10.1164/rccm.202111-2528ED
PMID: 34818134

81. **[MDR tuberculosis, Alpha-1-anti-trypsin Deficiency, Cough in a Geriatric Nurse].**

Pneumologie. 2021 Dec;75(12):971-980. doi: 10.1055/a-1493-1206. Epub 2021 Jul 7.

Hoheisel A(1), Vogt G(2), Nagel S(2), Bonitz A(3), Müller C(4), Köhnlein T(5), Hoheisel G(3).

Multidrug-resistant tuberculosis (MDR-TB) is of low proportion in comparison to the total number of TB patients, however, due to the necessity of a complex medication with potentially severe and life threatening adverse reactions, long term sequelae, and unfavorable outcome special attention is essential. We report the case of a 30-year-old geriatric nurse with a history of chronic cough and hereditary alpha-1-anti-trypsin deficiency (AATD), who suffered from MDR-TB and experienced a number of severe adverse reactions.

DOI: 10.1055/a-1493-1206
PMID: 34233361 [Indexed for MEDLINE]

82. **Rifampicin susceptibility discordance between Xpert MTB/RIF G4 and Xpert Ultra before MDRT-TB treatment initiation: A case report from Uganda.**

J Clin Tuberc Other Mycobact Dis. 2021 Nov 6;25:100286. doi: 10.1016/j.jctube.2021.100286. eCollection 2021 Dec.

Ssengooba W(1)(2), Komakech K(2), Namiiro S(1), Byabajungu H(3), Nalunjogi J(1), Katagira W(1), Kimuli I(1), Joloba ML(1)(2), Adakun S(1)(4), Nakiyingi L(5), Torrea G(6), Kirenga BJ(1).

Tuberculosis (TB) resistance to rifampicin, the most powerful drug leads to increase in mortality. Globally, half a million new patients develop such resistant TB each year, coupled with both inappropriate diagnosis and treatment initiation. We report a case of rifampicin resistant Mycobacterium tuberculosis

whose rifampicin resistance was missed by Xpert MTB/RIF Assay G4 but detected by the Xpert MTB/RIF Ultra assay at different time points leading to increased delays for MDR-TB treatment initiation at Mulago Hospital, Kampala, Uganda. Our case report compels greater urgency in accelerating the transition to the newer assay, Ultra, to benefit from higher sensitivity of rifampicin resistance detection.

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PMID: 34816021