August Literature

1. Drug-resistant Mycobacterium tuberculosis and its genotypes isolated from an outbreak in western Thailand.

Trans R Soc Trop Med Hyg. 2021 Aug 2;115(8):886-895. doi: 10.1093/trstmh/traa148.

Rudeeaneksin J(1), Phetsuksiri B(1), Nakajima C(2)(3), Bunchoo S(1), Suthum K(4), Tipkrua N(4), Fukushima Y(2), Suzuki Y(2)(3).

BACKGROUND: Multidrug-resistant TB (MDR-TB) outbreaks have occurred in the Thamaka district, Kanchanaburi province in Thailand.
METHODS: Seventy-two isolates, which included 7% mono-, 30.6% MDR and extensively drug-resistant TB (XDR-TB), were genotyped by spoligotyping, mycobacterial interspersed repetitive unit-variable-number tandem repeat (MIRU-VNTR) and single nucleotide polymorphism genotyping, and their drug resistance was analysed.
RESULTS: The spoligotyping results showed that Beijing spoligo-international type (SIT)1 was predominant (n=38; 52.8%) while the remaining were non-Beijing sublineages (n=34). The MIRU-VNTR analysis showed that Beijing isolates, most of which belonged to the modern type (n=37), formed 5 clusters and 13 individual patterns. In katG, only mutation Ser315Thr was identified. In rpoB, Ser531Leu was predominant, except for His526Arg and Leu533Pro, which were found in two isolates. A cluster of 14 Beijing strains contained these common mutations and shared the MIRU-VNTR genotype with isolates in the Thamaka district that had spread previously. Two U SIT523 isolates contained the mutations A1400G in rrs and Asp94Gly in gyrA genes, indicating a spread of XDR-TB.
CONCLUSIONS: Most mutations were associated with drug resistance and the specific MDR Beijing and XDR-TB in U SIT523 isolates remain. This genotyping is a key tool for tracking TB transmission in the Thamaka district of Thailand.

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DOI: 10.1093/trstmh/traa148
PMCID: PMC8326958
PMID: 33320938 [Indexed for MEDLINE]

2. **Pyrosequencing for diagnosis of multidrug and extensively drug-resistant tuberculosis: A systemic review and meta-analysis.**

J Clin Tuberc Other Mycobact Dis. 2021 Jun 29;24:100254. doi: 10.1016/j.jctube.2021.100254. eCollection 2021 Aug.

Getachew E(1)(2), Adebeta T(3), Gebrie D(1)(4), Charlie L(1), Said B(1)(5), Assefa DG(1)(6), Wanjiru CL(1), Zeleke ED(1)(7), Tesfahunei HA(1)(8), Abebe M(1)(9), Joseph M(1), Manyazewal T(1).

BACKGROUND: Multidrug and extensively drug-resistant tuberculosis (M/XDR-TB) pose major threats to global health. Diagnosis accuracy and delay have been the major drivers for the upsurge of M/XDR-TB. Pyrosequencing (PSQ) is a novel, real-time DNA sequencing for rapid detection of mutations associated with M/XDR-TB. We aimed to systematically synthesize the evidence on the diagnostic accuracy of PSQ for M/XDR-TB.
METHODS: We conducted an electronic search of PubMed, Embase, Biosis, Web of Science, and Google Scholar up to March 2020. We used the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies) tool to assess the quality of studies, the BRMA (bivariate random-effects meta-analysis) model to synthesize diagnostic accuracies, and the Rev-Man 5.4 software to perform the meta-analyses. We analyzed dichotomous data using the risk ratio (RR) with a 95% confidence interval. PROSPERO Registration ID: CRD42020200817.
RESULTS: The analysis included seven studies, with a total sample of 3,165. At 95% confidence interval, the pooled sensitivity and specificity of PSQ were 89.7 (CI: 83.5-93.8) and 97.8 (CI: 94.9-99.1) for Isoniazid, 94.6 (CI: 90.9-96.8) and 98.5 (CI: 96.5-99.3) for Rifampicin, 87.9 (CI: 81.2-92.4) and 98.8 (CI: 97.2-99.5) for Fluoroquinolone, 83.5 (CI: 72.8-90.5) and 99.4 (CI: 98.3-99.8) for Amikacin, 79 (CI: 67-8-87) and 97.9 (CI: 95.5-99) for Capreomycin, and 69.6 (CI: 57-79.8) and 98.2 (CI: 95.9-99.2) for Kanamycin. The overall pooled sensitivity and specificity were 85.8 (CI: 76.7-91.7) and 98.5 (CI: 96.5-99.3), respectively.
CONCLUSION: According to the pooled data, PSQ is highly sensitive and specific for detecting M/XDR-TB, both from clinical specimens and culture isolates, and within a shorter turnaround time. We suggest a continued synthesis of the evidence on the cost-effectiveness and technical feasibilities of PSQ in low-income countries context, including sub-Saharan Africa.

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PMCID: PMC8267485
PMID: 34278006

3. **HIV-associated tuberculosis.**

Int J STD AIDS. 2021 Aug;32(9):780-790. doi: 10.1177/0956462421992257. Epub 2021 Feb 20.

Hamada Y(1)(2), Getahun H(3), Tadesse BT(3), Ford N(4).

Tuberculosis (TB) remains a leading cause of morbidity and mortality among people living with HIV. HIV-associated TB disproportionally affects African countries, particularly vulnerable groups at risk for both TB and HIV. Currently available TB diagnostics perform poorly in people living with HIV; however, new diagnostics such as Xpert Ultra and lateral flow urine lipoarabinomannan assays can greatly facilitate diagnosis of TB in people living with HIV. TB preventive treatment has been underutilized despite its proven benefits independent of antiretroviral therapy (ART). Shorter regimens using rifapentine can support increased availability and scale-up. Mortality is high in people with HIV-associated TB, and timely initiation of ART is critical. Programs should provide decentralized and integrated TB and HIV care in settings with high burden of both diseases to improve access to services that diagnose TB and HIV as early as possible. The new prevention and diagnosis tools recently recommended by WHO offer an immense opportunity to advance our fight against HIV-associated TB. They should be made widely available and scaled up rapidly supported by adequate funding with robust monitoring of the uptake to advance global TB elimination.

DOI: 10.1177/0956462421992257
PMCID: PMC8236666
PMID: 33612015

4. **Experiences and needs of patients with MDR/XDR-TB: a qualitative study among Saharia tribe in Madhya Pradesh, Central India.**

BMJ Open. 2021 Aug 12;11(8):e044698. doi: 10.1136/bmjopen-2020-044698.

Nigam S(1), Sharma RK(2), Yadav R(1), Rao VG(1), Mishra P(1), Lingala MA(1), Bhat J(3).

BACKGROUND: Drug-resistant tuberculosis (DR-TB) continues to be a major public health threat posing a critical challenge to TB treatment and control worldwide. The present study was conducted among patients with DR-TB of the Saharia tribe residing in Madhya Pradesh state of Central India to document their experiences and needs, and to identify gaps for treatment adherence as this population is known to be poor because of migration and other factors.
METHODS: We conducted 16 in-depth interviews on purposively selected patients with DR-TB among the Saharia tribe using a predesigned open-ended in-depth

interview guide, which included questions on domains like general physical health, diagnosis, treatment adherence, side-effects of drugs and experience related to the health facility. Out of these interviews, various subthemes were extracted. The obtained qualitative data were subjected to thematic analysis.
RESULTS: The study helped to understand the experiences and needs of the patients with DR-TB in various stages from diagnosis to treatment. Also, there was the impact of factors like lack of education and awareness, poor living conditions and lack of healthcare facilities on predominance of the disease in the community. Poor access to a healthcare facility, high pill burden and related side-effects, longer duration of treatment, financial burden, misbeliefs and misconceptions were prominent issues posing a challenge to treatment adherence. The narratives pointed out their struggle at every stage be it with diagnosis, treatment initiation or treatment adherence.
CONCLUSION: It is paramount to address the needs and experiences of patients with DR-TB to develop a patient-centric and context-specific approach conducive to the sociocultural set-up of tribal people. This will scale down the attrition rate of tribal patients while adhering to the complete treatment process and reducing the high burden of TB among the Saharia community. In addition, tribal patients should be counselled at regular intervals to increase their confidence in the treatment.

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DOI: 10.1136/bmjopen-2020-044698
PMID: 34385228 [Indexed for MEDLINE]

5. **Ambient air pollutants, diabetes and risk of newly diagnosed drug-resistant tuberculosis.**

Ecotoxicol Environ Saf. 2021 Aug;219:112352. doi: 10.1016/j.ecoenv.2021.112352. Epub 2021 May 25.

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

BACKGROUND: Drug-resistant tuberculosis (DR-TB), diabetes and exposure to air pollution are thought to be important threat to human health, but no studies have explored the effects of ambient air pollutants on DR-TB when adjusting diabetes status so far.
METHODS: We performed a study among 3759 newly diagnosed TB cases with drug-susceptibility testing results, diabetes status, and individual air pollution data in Shandong from 2015 to 2019. Generalized linear mixed models

(GLMM) including three models (Model 1: without covariates, Model 2: adjusted by diabetes status only, Model 3: with all covariates) were applied.
RESULTS: Of 3759 TB patients enrolled, 716 (19.05%) were DR-TB, and 333 (8.86%) had diabetes. High exposure to O3 was associated with an increased risk of RFP-resistance (Model 2 or 3: odds ratio (OR) = 1.008, 95% confidence intervals (CI): 1.002-1.014), ethambutol-resistance (Model 3: OR = 1.015, 95%CI: 1.004-1.027) and any rifampicin+streptomycin resistance (Model 1,2,3: OR = 1.01, 95%CI: 1.002-1.018) at 90 days. In contrast, NO2 was associated with a reduced risk of DR-TB (Model 3: OR = 0.99, 95%CI: 0.981-0.999) and multidrug-resistant TB (MDR-TB) (Model 3: OR = 0.977, 95%CI: 0.96-0.994) at 360 days. Additionally, SO2 (Model 1, 2, 3: OR = 0.987, 95%CI: 0.977-0.998) showed a protective effect on MDR-TB at 90 days. PM2.5 (90 days, Model 2: OR = 0.991, 95%CI: 0.983-0.999), PM10 (360 days, Model 2: OR = 0.992, 95%CI: 0.985-0.999) had protective effects on any RFP+SM resistance.
CONCLUSIONS: O3 contributed to an elevated risk of TB resistance but PM2.5, PM10, SO2, NO2 showed an inverse effect. Air pollutants may affect the development of drug resistance among TB cases by adjusting the status of diabetes.

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PMID: 34044311 [Indexed for MEDLINE]

6. **Novel treatments in multidrug-resistant tuberculosis.**

Curr Opin Pharmacol. 2021 Aug;59:103-115. doi: 10.1016/j.coph.2021.05.007. Epub 2021 Jun 26.

Mondoni M(1), Saderi L(2), Sotgiu G(3).

The management of multidrug-resistant tuberculosis (TB) is associated with low treatment success, high mortality and failure rates. New drugs and novel short-therapeutic regimens have only recently helped overcome these obstacles. We carried out a narrative literature review aimed at summarizing the scientific evidence on the recent therapeutic advances in the field of drug-resistant TB. Experimental and observational studies on novel (i.e. bedaquiline, delamanid, pretomanid) drugs and novel regimens and the main pharmacological characteristics of the newest compounds are described. We also highlight the main scientific evidence on therapeutic strategies complementary to standard chemotherapy (i.e. new approaches to drug delivery, host-directed therapy, surgery, new collapse therapy, rehabilitation, and palliative care).

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DOI: 10.1016/j.coph.2021.05.007
PMID: 34186381

7. **Individualised treatment for multidrug-resistant tuberculosis in New South Wales, Australia.**

Aust N Z J Public Health. 2021 Jul 26. doi: 10.1111/1753-6405.13144. Online ahead of print.

Chang V(1)(2), Ling R(1), Velen K(1), Fox G(1)(3).

OBJECTIVE: Multidrug-resistant tuberculosis (MDR-TB) presents a major global health challenge. In high-income countries, treatment is individualised to optimise efficacy and reduce toxicity. We aimed to evaluate the outcomes of patients with MDR-TB receiving individualised antibiotic therapy in Australia.
METHODS: This retrospective cohort study was performed in the city of Sydney in Australia and included patients diagnosed with bacteriologically confirmed MDR-TB diagnosed between 2000 and 2016. The clinical characteristics of patients and treatment details were extracted from medical records. The incidence of adverse events and end-of-treatment outcomes were also evaluated.
RESULTS: Fifty-five patients with MDR-TB were identified at TB clinics in seven hospitals. The median age was 32 years (interquartile range [IQR]: 27-36 years). The median duration of the intensive phase treatment was six months (IQR 6-7 months). All patients' treatment administration was directly observed. The commonest reported adverse event was ototoxicity (44%; 23/52) and successful treatment outcomes were achieved by 95% (52/55) of patients.
CONCLUSION: This study demonstrated the high treatment success rate that can be achieved using individualised treatment for MDR-TB in a well-resourced setting. Implications for public health: The expansion of individualised therapy promises to contribute to MDR-TB control and advance the ambitious goal of TB elimination by 2035.

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PMID: 34309967

8. **Editorial: Updates from the World Health Organization (WHO) on Global Treatment Recommendations for Drug-Susceptible and Multidrug-Resistant Tuberculosis.**

Med Sci Monit. 2021 Aug 9;27:e934292. doi: 10.12659/MSM.934292.

Parums DV(1).

The World Health Organization (WHO) estimated that in 2019, 10.0 million people worldwide developed tuberculosis (TB), with 1.4 million deaths from TB in that year. Infection with Mycobacterium tuberculosis that is resistant to at least isoniazid and rifampin and an additional chemotherapeutic agent is known as multidrug-resistant TB (MDR TB). Until recently, the prevalence of drug resistance in patients with TB has been poorly understood due to a lack of infection surveillance and molecular testing. Countries with the highest prevalence of TB, including MDR TB, are also those most affected by the COVID-19 pandemic. The identification of MDR TB requires careful monitoring and resources for molecular testing. Previous treatment regimens have required intravenous treatments of long duration and high cost. The 2020 and 2021 recommendations from the WHO for the management of drug-susceptible TB and MDR TB have included oral treatment regimens and reduced treatment duration. This Editorial aims to present the rationale for the 2020 and 2021 recommendations from the WHO for the management of drug-susceptible TB and MDR TB.

DOI: 10.12659/MSM.934292
PMID: 34366429 [Indexed for MEDLINE]

9. **Identification and attribute analysis of key stakeholders who influence multidrug-resistant tuberculosis prevention and control in China.**

Infect Dis Poverty. 2021 Aug 12;10(1):108. doi: 10.1186/s40249-021-00892-7.

Chen B(1)(2), Bao H(3), Chen X(2), Liu K(2), Peng Y(2), Wang W(2), Wang F(2), Jiang J(2)(4), Xu B(5)(6).

BACKGROUND: There could be various stakeholders who influencing multidrug-resistant tuberculosis (MDR-TB) policy development and implementation, yet their attributes and roles remain unclear in practice. This study aimed to identify key stakeholders in the process of policy-making for MDR-TB control and prevention and to analyse the attributes and relationships of the stakeholders, providing evidence for further policy research on MDR-TB control.
METHODS: This study was conducted from October 2018 to March 2019 and applied the stakeholder analysis guidelines and domestic stakeholder analysis. An initial candidate stakeholder list was developed by policy scanning. Ten experts were invited to identify these candidate stakeholders. The major attribute of these stakeholders were analysed using the Michell scoring method. Based on these results, the intertwined relationships among groups of stakeholders were

analysed and mapped through a systematic scan of the policy and literature on MDR-TB control, as well as information obtained from the interviews.
RESULTS: A list of 21 types of candidate stakeholders was developed after a literature review and policy scanning, of which 11 received 100% approval. After expert evaluation and identification (the total expert authority was 0.80), 19 categories of stakeholders were approved and included in the stakeholder analysis. We categorized all of the stakeholders into three groups: (i) definitive stakeholders who are mainly involved in administrative departments and the Provincial Center for Disease Control and Prevention (CDC); (ii) expectant stakeholders who are mainly involved with MDR-TB patients, clinical departments of TB hospitals at different levels, community health care facilities, prefectural CDC and charity organizations; and (iii) latent stakeholders who mainly involved family members and neighbours of MDR-TB patients and TB related products manufacturers. Government departments and higher-level CDCs have strong decision-making power in developing MDR-TB control policies whereas the recommendations from service providers and the concerns of patients should be considered.
CONCLUSIONS: The MDR-TB prevention system was a multistakeholder cooperation system that was mainly led by government stakeholders. Enhancing communications with front-line service providers and patients on their unmet needs and evidence-based suggestions would highly benefit policy-making of MDR-TB prevention and control.

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PMCID: PMC8359086
PMID: 34384503

10. **Spectrum of Drug Resistance in Musculoskeletal Tuberculosis.**

Indian J Orthop. 2021 Mar 1;55(4):907-911. doi: 10.1007/s43465-021-00378-6. eCollection 2021 Aug.

Sural S(1), Soni A(1), Kashyap A(1), Ahmad V(2), Hanif M(2), Khanna A(3).

BACKGROUND: Very few studies report resistance pattern exclusively in musculoskeletal tuberculosis (MSK-TB).
METHODS: This study of 100 pus samples from patients of MSK-TB with active disease in whom Mycobacterium tuberculosis (MTB) was detected by cartridge-based nucleic acid amplification test (CBNAAT), revealed the pattern of resistance among newly diagnosed and previously treated cases. Liquid culture and drug susceptibility testing (DST) using MGIT 960 was done for 11 anti-tubercular

drugs.
RESULTS: Among these 100 cases; 22% were AFB positive; MGIT 960 detected MTB in 58.33% (35/60) new cases and 30.0% (12/40) previously treated cases. Five new and 10 previously treated cases had drug resistance and 12 were detected rifampicin resistance (Rif-R) by CBNAAT. Among new cases MGIT-DST detected mono-INH resistant in 2.86% (1/35), mono-STR resistant in 2.86% (1/35), MDR-TB in 5.7% (2/35) and pre-XDR in 2.9%(1/35).Among previously treated cases Rif-R was found in 10% (4/40) where MTB was not detected by MGIT and MGIT-DST detected mono-INH resistant in 8.33% (1/12); MDR-TB in 8.33% (1/12) and pre-XDR in 33.3%. There were no cases of XDR-TB.
CONCLUSION: High disease burden of various type drug resistance were seen more commonly in previously treated cases and was not uncommon in new cases of MSK-TB. Both CBNAAT and DST are essential for detecting resistance pattern in MSK-TB.

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DOI: 10.1007/s43465-021-00378-6
PMCID: PMC8192612
PMID: 34194646

11. **Impact of the revised definition of extensively drug-resistant tuberculosis.**

Eur Respir J. 2021 Aug 19;58(2):2100641. doi: 10.1183/13993003.00641-2021. Print 2021 Aug.

Veziris N(1), Bonnet I(2), Morel F(2), Guglielmetti L(2), Maitre T(3), Fournier Le Ray L(3), Sougakoff W(2), Robert J(2), Aubry A(2); CNR MyRMA; Members of the CNR-MyRMA (French National Reference Center for Mycobacteria.

Collaborators: Cambau E, Mougari F, Ok V.

Recently, the World Health Organization (WHO) has released a revised definition of extensively drug-resistant (XDR) tuberculosis (TB) that should be used for clinical and surveillance purposes starting from 1 January, 2021 [1, 2]. The previous definition of XDR-TB was TB that is resistant to any fluoroquinolone (levofloxacin and/or moxifloxacin) and to at least one of three second-line injectable drugs (SLIs: capreomycin, kanamycin and amikacin), in addition to multidrug resistance. The revised definition is: TB caused by Mycobacterium tuberculosis strains that fulfil the definition of MDR/RR-TB and which are also resistant to any fluoroquinolone and at least one additional group A drug. WHO group A drugs currently include fluoroquinolones (levofloxacin or moxifloxacin), linezolid and bedaquiline. In addition, pre-XDR-TB is now a WHO-endorsed definition, identified as MDR/RR-TB with any fluoroquinolone resistance. Although the previous definition of XDR-TB has proved to be predictive of poor treatment outcome [3],

the 2020 update appears in line with recent changes of treatment regimens given, i.e. less frequent use of SLI in favour of the potent oral drugs, bedaquiline and linezolid. Moreover, a large meta-analysis failed to show an association between mortality reduction and SLI use, whereas this association was shown for bedaquiline and linezolid [4]. In this study, we aimed to measure retrospectively the impact of the revised definition on the epidemiology of XDR-TB in France.

DOI: 10.1183/13993003.00641-2021
PMID: 33926973

12. **Pattern of Drug Resistance in Primary Spinal Tuberculosis: A Single-Center Study From India.**

Global Spine J. 2021 Sep;11(7):1070-1075. doi: 10.1177/2192568220941445. Epub 2020 Aug 17.

Bhosale S(1), Prabhakar A(2), Srivastava S(1), Raj A(1), Purohit S(1), Marathe N(1).

STUDY DESIGN: Retrospective observational analysis.
OBJECTIVES: Spinal tuberculosis accounts for about 50% of cases among extra pulmonary osteoarticular tuberculosis. Resistance to drugs in spinal tuberculosis patients is on a rise and there is inadequate literature concentrating on the precise pattern of resistance in Indian subcontinent which harbors 24% of global prevalence. The aim was to study the pattern of drug resistance in spinal tuberculosis among first- and second-line drugs. Drug resistance is common in spinal tuberculosis and we intended to find the prevalence of various drug resistance patterns.
METHODS: Patients with spinal tuberculosis visiting a tertiary center were assessed. Samples were taken from the affected vertebrae and sent for BACTEC mycobacterium growth indicator tube (MGIT) 960 culture. Patients with a positive growth in MGIT were included in the study. All previously treated patients (relapse, treatment after failure, treatment after loss to follow-up and other previously treated patients) were excluded.
RESULTS: A total of 150 patients with a positive growth in MGIT report were included in the study, of whom 43 patients had some kind of drug resistance. Seven were multidrug resistant (MDR), 9 had preextensive drug resistance (pre-XDR), and 4 had extensive drug resistance (XDR). Seventeen patients had mono-drug resistance, which was most frequently for isoniazid. Resistance among second-line drugs was common in the fluoroquinolone group.
CONCLUSION: Drug resistance in spinal tuberculosis was found to be 28.6%. Of these, MDR was in 16.2%, pre-XDR in 20.9%, and XDR in 9.3% patients.

DOI: 10.1177/2192568220941445
PMCID: PMC8351075
PMID: 34343039

13. **National treatment outcome and predictors of death and treatment failure in multidrug-resistant tuberculosis in Ethiopia: a 10-year retrospective cohort study.**

BMJ Open. 2021 Aug 10;11(8):e040862. doi: 10.1136/bmjopen-2020-040862.

Tola H(1)(2), Holakouie-Naieni K(3), Mansournia MA(1), Yaseri M(1), Gamtesa DF(2), Tesfaye E(2), Mahamed Z(2), Sisay MM(4).

OBJECTIVES: Treatment success rate in patients treated for multidrug-resistant tuberculosis (MDR-TB) is low, but predictors of treatment failure and death have been under-reported. Thus, we aimed to determine the national proportion of treatment success rate in the past 10 years and factors that predict treatment failure and death in patients with MDR-TB in Ethiopia.
SETTING: A retrospective cohort study with a 10-years follow-up period was conducted in 42 MDR-TB treatment-initiating centres in Ethiopia.
PARTICIPANTS: A total of 3395 adult patients with MDR-TB who had final treatment outcome and who were treated under national TB programme were included. Data were collected from clinical charts, registration books and laboratory reports. Competing risk survival analysis model with robust standard errors (SE) was used to determine the predictors of treatment failure and death.
PRIMARY AND SECONDARY OUTCOMES: Treatment outcome was a primary outcome whereas predictors of treatment failure and death were a secondary outcome.
RESULTS: The proportion of treatment success was 75.7%, death rate was 12.8%, treatment failure was 1.7% and lost to follow-up was 9.7%. The significant predictors of death were older age (adjusted hazard ratio (AHR)=1.03; 95% CI 1.03 to 1.05; p<0.001), HIV infection (AHR=2.0; 95% CI 1.6 to 2.4; p<0.001) and presence of any grade of anaemia (AHR=1.7; 95% CI 1.4 to 2.0; p<0.001). Unlike the predictors of death, all variables included into multivariable model were not significantly associated with treatment failure.
CONCLUSION: In the past 10 years, although MDR-TB treatment success in Ethiopia has been consistently favourable, the proportion of patients who died is still considerable. Death could be attributed to advanced age, HIV infection and anaemia. Prospective cohort studies are necessary to further explore the potentially modifiable predictors of treatment failure.

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DOI: 10.1136/bmjopen-2020-040862
PMID: 34376436 [Indexed for MEDLINE]

14. **Analysis of CD4 and CD8 expression in multidrug-resistant tuberculosis infection with diabetes mellitus: An experimental study in mice.**

Ann Med Surg (Lond). 2021 Jul 27;68:102596. doi: 10.1016/j.amsu.2021.102596. eCollection 2021 Aug.

Agustin H(1)(2)(3), Massi MN(4), Djaharuddin I(5), Susanto AD(2)(3), Islam AA(6), Hatta M(7), Bukhari A(8), Tabri NA(5), Santoso A(5), Patellongi I(9).

BACKGROUND: Tuberculosis (TB) remains a major global health problem, in the top 10 causes of death. As a regulator of the immune response, T-helper (Th) cells activate other lymphocytes from the immune system, such as B cells, to destroy the TB pathogen by releasing CD4 and CD8 Th cells. Diabetes mellitus (DM) is a known cause of developing active pulmonary TB. Few studies have examined the biomolecular expression affecting Mycobacterium tuberculosis (MTB) and multidrug-resistant (MDR) MTB, which are associated with low immunity represented by TB in diabetes and CD4 and CD8 levels.
MATERIALS AND METHODS: This animal study used a post-test control group design. We performed an experimental study using 30 BALB/c mice, each weighing 25 g. It included six experimental animal groups, of which three had a diabetes condition induced using intraperitoneal streptozotocin, and all were infected with MTB or MDR TB. We evaluated the CD4 and CD8 levels in each group and analyzed the differences.
RESULTS: We found a significant difference in CD4 and CD8 levels in MTB and MDR TB conditions.
CONCLUSION: This study shows that acute infection in experimental mice with MTB and MDR TB with or without diabetes had the highest levels of both CD4 and CD8 cells, which can be a sign of increased cellular immunity in a mice model.

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PMCID: PMC8350178
PMID: 34401121

15. **A highly effective and inexpensive standardized treatment of multidrug-resistant tuberculosis: a multicenter prospective study in China.**

BMC Infect Dis. 2021 Aug 19;21(1):834. doi: 10.1186/s12879-021-06553-2.

Sun W(1), Wu Z(2), Zhou Y(3), Xia F(4), Tang Q(1), Wang J(5), Yang J(6), Yu F(6), Yang H(5), Xiao H(7), Fan L(8).

BACKGROUND: To verify the efficacy and safety of an inexpensive standardized regimen for multidrug-resistant tuberculosis (MDR-TB) with low resistance to isoniazid (INH), a multicenter prospective study was conducted in eastern China.
METHODS: Patients diagnosed as MDR-TB with low concentration INH resistance and rifampicin resistance, second-line/injectable agents sensitive were prospectively enrolled, given the regimen of Amikacin (Ak)-Fluoroquinolones (FQs)-Cycloserine (Cs)-Protionamide (Pto)-PasiniaZid (Pa)-Pyrazinamide (Z) for 6 months followed by 12 months of FQs-Cs-Pto-Pa-Z, and then followed up for treatment outcomes and adverse events (AEs).
RESULTS: A total of 114 patients were enrolled into the study. The overall favorable treatment rate was 79.8% (91/114). Among 91 cases with favorable treatment, 75.4% (86/114) were cured and 4.4% (5/114) were completed treatment. Regarding to unfavorable outcomes, among 23 cases, 8.8% (10/114) had failures, 8.8% (10/114) losing follow up, 0.9% (1/114) had treatment terminated due to intolerance to drugs and 1.8% (2/114) died. Treatment favorable rate was significantly higher in newly treated MDR-TB (91.7%, 33/36) than that in retreated MDR-TB (74.4%, 58/78, p 0.03). The investigators recorded 42 AEs occurrences in 30 of 114 patients (26.3%). Clinicians rated most AEs as mild or moderate (95.24%, 40/42).
CONCLUSIONS: The regimen was proved to be effective, safe and inexpensive. It is suitable for specific drug resistant population, especially for newly-treated patients, which could be expected to be developed into a short-course regimen. Clinical trials registration China Clinical Trial Registry ChiCTR-OPC-16009380.

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DOI: 10.1186/s12879-021-06553-2
PMID: 34412615

16. **Exploratory development of PCR-fluorescent probes in rapid detection of mutations associated with extensively drug-resistant tuberculosis.**

Eur J Clin Microbiol Infect Dis. 2021 Sep;40(9):1851-1861. doi: 10.1007/s10096-021-04236-z. Epub 2021 Apr 1.

Liang J(#)(1), An H(#)(1), Zhou J(#)(1), Liu Y(#)(2), Xiang G(3), Liu Y(3), Xing W(4)(5)(6), Gong W(7).

This study aims to evaluate the clinical value of PCR-fluorescent probes for

detecting the mutation gene associated with extensively drug-resistant tuberculosis (XDR-TB). The molecular species identification of 900 sputum specimens was performed using polymerase chain reaction (PCR)-fluorescent probe. The mutations of the drug resistance genes rpoB, katG, inhA, embB, rpsL, rrs, and gyrA were detected. The conventional drug susceptibility testing (DST) and PCR-directed sequencing (PCR-DS) were carried out as control. DST demonstrated that there were 501 strains of rifampicin resistance, 451 strains of isoniazid resistance, 293 strains of quinolone resistance, 425 strains of streptomycin resistance, 235 strains of ethambutol resistance, and 204 strains of amikacin resistance. Furthermore, 427 (47.44%) or 146 (16.22%) strains were MDR-TB or XDR-TB, respectively. The mutations of the rpoB, katG, inhA, embB, rpsL, rrs, and gyrA genes were detected in 751 of 900 TB patients by PCR-fluorescent probe method, and the rate of drug resistance was 751/900 (83.44%). No mutant genes were detected in the other 149 patients. Compared with DST, the mutant rates of rpoB, katG/inhA, rpsL, rrs, embB, and gyrA of six drugs were higher than 88%; five of six drugs were higher than 90% except for SM (88.11%). The MDR and XDR mutant gene types were found in 398 (42.22%) and 137 (15.22%) samples. PCR-DS was also employed and confirmed the PCR-fluorescent probe method with the accordance rate of 100%. The PCR-fluorescent probe method is rapid and straightforward in detecting XDR-TB genotypes and is worthy of being applied in hospitals.

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DOI: 10.1007/s10096-021-04236-z
PMID: 33792806

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

Eur J Cardiothorac Surg. 2021 Jul 23:ezab337. doi: 10.1093/ejcts/ezab337. Online ahead of print.

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.

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DOI: 10.1093/ejcts/ezab337
PMID: 34297819

18. **A Semi-Mechanistic Model of the Bactericidal Activity of High-Dose Isoniazid Against Multi-Drug-Resistant Tuberculosis: Results from a Randomized Clinical Trial.**

Am J Respir Crit Care Med. 2021 Aug 17. doi: 10.1164/rccm.202103-0534OC. Online ahead of print.

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)(8), Swindells S(9), Diacon AH(6), Nuermberger EL(10), Dooley KE(10), Denti P(11); A5312 Study Team.

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.
OBJECTIVE: Characterizing 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 A5312/INHindsight is 7-day early bactericidal activity study with isoniazid at 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 TB received daily isoniazid monotherapy and collected sputum daily. Colony-forming units (CFU) on solid culture and time-to-positivity (TTP) in liquid culture were jointly analyzed using nonlinear mixed-effects modeling.
RESULTS: Fifty-nine adults were included in this analysis. Decline in sputum CFU was described by a one-compartment model, while an exponential bacterial growth model was used to interpret TTP data. The model found bacterial kill is modulated by isoniazid concentration using an effect compartment and a sigmoidal Emax relationship. The model predicted lower potency but similar maximum-kill of isoniazid against inhA-mutated isolates compared to drug-sensitive. Based on simulations from the PK/PD model, to achieve a drop in bacterial load comparable to 5mg/kg against drug-sensitive TB, 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 while mitigating toxicity risks associated with higher doses. Clinical trial registration available at www.clinicaltrials.gov, ID: NCT01936831.

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

19. **Novel candidates in the clinical development pipeline for TB drug development and their Synthetic Approaches.**

Chem Biol Drug Des. 2021 Aug 15. doi: 10.1111/cbdd.13934. Online ahead of print.

Kumar A(1), Karkara BB(1)(2), Panda G(1).

Tuberculosis (TB) is an infection caused by Mycobacterium tuberculosis (Mtb) and one of the deadliest infectious diseases in the world. Mtb has the ability to become dormant within the host and to develop resistance. Hence, new antitubercular agents are required to overcome problems in the treatment of multidrug resistant-Tb (MDR-Tb) and extensively drug resistant-Tb (XDR-Tb) along with shortening the treatment time. Several efforts are being made to develop very effective new drugs for Tb, within the pharmaceutical industry, the academia, and through public private partnerships. This review will address the anti-tubercular activities, biological target, mode of action, synthetic approaches and thoughtful concept for the development of several new drugs

currently in the clinical trial pipeline (up to October 2019) for tuberculosis. The aim of this review may be very useful in scheming new chemical entities (NCEs) for Mtb.

DOI: 10.1111/cbdd.13934
PMID: 34397161

20. **Synthetic molecules as DprE1 inhibitors: A patent review.**

Expert Opin Ther Pat. 2021 Aug;31(8):759-772. doi: 10.1080/13543776.2021.1902990. Epub 2021 Apr 13.

Imran M(1), A S A(2), Thabet HK(3), Abida(1), Afroz Bakht M(4).

INTRODUCTION: In recent years, the advent of multidrug-resistant tuberculosis (MDR-TB), the extensively-resistant TB (XDR-TB), and the total drug-resistant-TB (TDR-TB) have led the community to develop new antitubercular molecules. The decaprenylphosphoryl-β-D-ribose-2'-epimerase-1 (DprE1) is an established target to developed new anti-TB drugs. This enzyme is required to synthesize the cell wall of Mycobacterium tuberculosis (Mtb).
AREA COVERED: This patent review focuses on the granted patents and patent applications related to the chemical entities developed as DprE1 inhibitors for TB treatment from the publication year of the BTZ-043 compound patent application (2007) till 30 September 2020.
EXPERT OPINION: The DprE1 has many advantages in the development of new antitubercular molecules, for example, its location in the periplasm of the Mtb cell wall and its absence in the human body. This indicates that the DprE1 inhibitors are selective for Mtb, and their toxic and side effects on the human body may be negligible or small. Accordingly, the use of DprE1 inhibitors may be benefic for patients with drug-resistant bacteria that require long-term medication. Four molecules are in clinical trials, which could become the drugs of the future for TB-therapy.

DOI: 10.1080/13543776.2021.1902990
PMID: 33709862 [Indexed for MEDLINE]

21. **Early detection of MDR Mycobacterium tuberculosis mutations in Pakistan.**

Sci Rep. 2021 Aug 18;11(1):16736. doi: 10.1038/s41598-021-96116-x.

Aftab A(1), Afzal S(2), Qamar Z(1), Idrees M(1).

The result of improper treatment has led to the rise of Multidrug-resistant (MDR) strains. This concern still exists in Pakistan. In order to save energy, time and resources an early detection of resistant cases is imperative. Thus, a treated group of 100 isolates and a control group of 56 untreated isolates were studied. PCR and gene sequencing showed mutations at codon 531 and 513 in the rpoB gene. 12% of cases showed a double mutation in the rpoB gene. katG gene showed mutations at codon 315 and 299. 28.6% of the control group cases were positive for MDR whereas 100% of the treated group were positive for MDR. This study explores the significantly increasing ratio of MDR-TB among Pakistani population. This study provides prevalent MDR mutations among Pakistanis and suggests developing such molecular assays that are time and cost effective. Importance: Pakistan is a developing country and has fourth highest incidence rate of MDR-TB. The treatment of MDR-TB is the use of second line drugs that has severe side effects as well as it requires long time span. One of the strategies to control the spread of MDR-TB is to decipher the aberrations at molecular level in order to formulate potent drugs that can treat the patients within short span of time. Determining the mutation profile of MDR in Pakistani populations will open new horizons for the improvement of drug treatment regimens to make it more effective or for the development of novel potent drugs and vaccines to better treat the drug-resistant TB. Moreover, this study will be help in disease control program.

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DOI: 10.1038/s41598-021-96116-x
PMID: 34408186

22. **The effect of isoniazid intake on ethionamide pharmacokinetics and target attainment in multidrug-resistant tuberculosis patients.**

Antimicrob Agents Chemother. 2021 Jul 26:AAC0027821. doi: 10.1128/AAC.00278-21. Online ahead of print.

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

Ethionamide is recommended as part of regimens to treat multidrug-resistant and rifampicin-resistant tuberculosis. The study was conducted to (i) describe the distribution of ethionamide minimum inhibitory concentrations (MICs), (ii) describe the pharmacokinetics of ethionamide, and (iii) determine the probability of attaining target AUC0-24/MIC values associated with suppression of resistant subpopulation and microbial kill. Participants received 15-20 mg/kg of ethionamide daily (in 500 or 750 mg doses), as part of a multidrug regimen.

Pretreatment MICs of ethionamide for M. tuberculosis sputum isolates were determined using Sensititre MYCOTB MIC plates. Plasma concentrations of ethionamide (measured pre-dose and at 2, 4, 6, 8 and 10 hours post-dose) were available for 84 patients. A one-compartment disposition model including a liver compartment capturing hepatic extraction, best described ethionamide pharmacokinetics. Clearance and volume were allometrically scaled using fat-free mass. Isoniazid co-administration reduced ethionamide clearance by 31% resulting in a 44% increase in AUC0-24. The median (range) MIC (n=111) was 2.5 mg/L (<0.3 to >40 mg/L). Simulations showed increased daily doses of ethionamide (1 250 mg, 1 500 mg, and 1 750 mg for patients weighing ≤45 kg, 46-70 kg, and >70 kg, respectively) resulted in the probability of attaining a fAUC0-24/MIC ratio ≥ 42 in more than 90% of patients, only at the lowest MIC of 0.3 mg/L. The WHO recommended doses of ethionamide do not achieve target concentrations even for the lowest MIC measured in the cohort.

DOI: 10.1128/AAC.00278-21
PMID: 34310215

23. **The Reductionist Conundrum of an "Updated" Definition of Extensively Drug-resistant Tuberculosis.**

Am J Respir Crit Care Med. 2021 Aug 10. doi: 10.1164/rccm.202106-1516ED. Online ahead of print.

Mitnick CD(1), Furin JJ(2), Hewison C(3).

In September 2006, newspapers announced the arrival of “killer strains” of tuberculosis (TB). “Extensively drug-resistant tuberculosis” or “XDR-TB” as it was later known, gained notoriety following a deadly outbreak in rural KwaZulu-Natal, South Africa. Of the 53 people with the disease, 52 perished quickly.1 Most had been living with HIV, had experienced prolonged diagnostic delays and sub-optimal therapeutic regimens, and had inadequate psychosocial and socioeconomic support. However, the humans and their illness experience were forgotten as the global public health community focused on one aspect—the drug susceptibility profile of the infecting organisms.2 XDR-TB came to be defined as disease caused by strains of Mycobacterium tuberculosis with in vitro resistance to isoniazid and rifampicin (multidrug-resistant [MDR] TB) and to the fluoroquinolones and injectable agents, the backbone of MDR-TB treatment at the time.3

DOI: 10.1164/rccm.202106-1516ED
PMID: 34375572

24. **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 Jul 23. doi: 10.1007/s10096-021-04316-0. Online ahead of print.

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.

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

25. **Assessment of the GenoType MTBDRsl VER 2.0 compared to the phenotypic drug susceptibility testing and whole genome sequencing for the rapid detection of resistance to fluoroquinolone and second-line injectable drugs among rifampicin-resistant Mycobacterium tuberculosis isolates.**

Arch Microbiol. 2021 Sep;203(7):3989-3996. doi: 10.1007/s00203-021-02387-3. Epub 2021 May 25.

Kardan-Yamchi J(1)(2), Amini S(3), Hamzelou G(3), Rahimi Foroushani A(4), Ghodousi A(5), Cirillo DM(5), Feizabadi MM(6)(7).

Molecular techniques have considerable advantages for rapid detection, a reduction of infectiousness, prevention of further resistance development and surveillance of drug-resistant TB. MTBDRsl VER 2.0 was used to detect resistance to second-line anti-tuberculosis drugs on 35 rifampicin-resistant M. tuberculosis (RR-MTB) isolates compared to the minimum inhibitory concentrations (MICs) and whole genome sequencing (WGS). The MTBDRsl VER 2.0 (Hain Life Science, Nehren, Germany) and WGS (San Diego, CA, USA) were performed for tracing mutations in resistant-related genes involved in resistance to fluoroquinolone (FLQ) and second-line injectable drugs. The broth microdilution method using 7H9 Middlebrook media supplemented with OADC was used to determine the MICs. The MTBDRsl VER 2.0 correctly detected 5/6 (83.3%) of FLQ-resistant strains. The MUT1 A1401G (seven strains) and MUT2 G1484T (one strain) mutations in rrs gene were detected in eight AMK/KAN/CAP-resistant strains. Four low-level KAN-resistant strains with the G-10A/C-12T (three strains) and eis C-14T (one strain) mutations in eis gene was diagnosed using MTBDRsl VER 2.0. Five errors were found in detecting resistance to kanamycin and capreomycin compared to the phenotypic drug susceptibility testing and WGS. Failling wild-type bands without improved mutant bands did not indicate a reliable resistance. WGS could efficiently resolve the discrepancies of the results. MTBDRsl showed better performance in detecting XDR strains than pre-XDR.

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DOI: 10.1007/s00203-021-02387-3
PMID: 34032874

26. **Bipolar Distribution of Minimum Inhibitory Concentration of Q203 Across Mycobacterial Species.**

Microb Drug Resist. 2021 Aug;27(8):1013-1017. doi: 10.1089/mdr.2020.0239. Epub 2021 Feb 26.

Wang J(1), Jing W(1), Shi J(1), Huo F(2), Shang Y(2), Wang F(2), Chu N(1), Pang Y(2).

In this study, we conducted an experimental study to evaluate in vitro

susceptibility of Q203 against Mycobacterium tuberculosis, as well as the major pathogenic nontuberculous mycobacterial species. A total of 344 nonduplicate mycobacterium isolates were randomly selected for in vitro susceptibility testing. Overall, Q203 exhibited excellent activity against multidrug-resistant (MDR-) and extensively drug-resistant tuberculosis (XDR-TB) isolates, whereas it showed high minimum inhibitory concentration (MIC) values for all nontuberculous mycobacteria (NTM) isolates tested. The MIC50 and MIC90 values were both 0.008 mg/L for MDR- and XDR-TB isolates, respectively. In contrast, the MIC50 and MIC90 values of four NTM species were all >16 mg/L. QcrB of M. tuberculosis, a component of the CytBC1 complex of the respiratory chain targeted by Q230, shared 89.7% amino acid sequence identity with Mycobacterium avium QcrB, 87.9% with that of Mycobacterium intracellulare, and 84.0% with that of Mycobacterium fortuitum, whereas with low sequence identity observed in QcrB sequence of Mycobacterium abscessus. Notably, the QcrBs of M. avium and M. intracellulare contained a 10-amino acid insertion in the linker between the eighth and ninth helical region. In conclusion, our data demonstrate the bipolar distribution of Q203 MICs across mycobacterial species. Compared with the high MICs in four clinically relevant mycobacterial species, MDR- and XDR-TB isolates have extremely low MICs, indicating that Q203 is a particularly promising candidate for TB treatment. In addition, the 10-amino acid insertion within QcrBs of M. avium and M. intracellulare may be a plausible explanation for the natural resistance to Q203 among these two species.

DOI: 10.1089/mdr.2020.0239
PMID: 33646044

27. **The Relevance of Genomic Epidemiology for Control of Tuberculosis in West Africa.**

Front Public Health. 2021 Jul 23;9:706651. doi: 10.3389/fpubh.2021.706651. eCollection 2021.

Asare P(1), Asante-Poku A(1), Osei-Wusu S(1), Otchere ID(1), Yeboah-Manu D(1).

Tuberculosis (TB), an airborne infectious disease caused by Mycobacterium tuberculosis complex (MTBC), remains a global health problem. West Africa has a unique epidemiology of TB that is characterized by medium- to high-prevalence. Moreover, the geographical restriction of M. africanum to the sub-region makes West Africa have an extra burden to deal with a two-in-one pathogen. The region is also burdened with low case detection, late reporting, poor treatment adherence leading to development of drug resistance and relapse. Sporadic studies conducted within the subregion report higher burden of drug resistant TB (DRTB) than previously thought. The need for more sensitive and robust tools for

routine surveillance as well as to understand the mechanisms of DRTB and transmission dynamics for the design of effective control tools, cannot be overemphasized. The advancement in molecular biology tools including traditional fingerprinting and next generation sequencing (NGS) technologies offer reliable tools for genomic epidemiology. Genomic epidemiology provides in-depth insight of the nature of pathogens, circulating strains and their spread as well as prompt detection of the emergence of new strains. It also offers the opportunity to monitor treatment and evaluate interventions. Furthermore, genomic epidemiology can be used to understand potential emergence and spread of drug resistant strains and resistance mechanisms allowing the design of simple but rapid tools. In this review, we will describe the local epidemiology of MTBC, highlight past and current investigations toward understanding their biology and spread as well as discuss the relevance of genomic epidemiology studies to TB control in West Africa.

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PMCID: PMC8342769
PMID: 34368069 [Indexed for MEDLINE]

28. **Pharmacokinetics and Target Attainment of SQ109 in Plasma and Human-Like Tuberculosis Lesions in Rabbits.**

Antimicrob Agents Chemother. 2021 Aug 17;65(9):e0002421. doi: 10.1128/AAC.00024-21. Epub 2021 Aug 17.

Egbelowo O(1), Sarathy JP(2), Gausi K(1), Zimmerman MD(2), Wang H(2), Wijnant GJ(2), Kaya F(2), Gengenbacher M(2), Van N(3), Degefu Y(3), Nacy C(4), Aldridge BB(3), Carter CL(2), Denti P(1), Dartois V(2)(5).

SQ109 is a novel well-tolerated drug candidate in clinical development for the treatment of drug-resistant tuberculosis (TB). It is the only inhibitor of the MmpL3 mycolic acid transporter in clinical development. No SQ109-resistant mutant has been directly isolated thus far in vitro, in mice, or in patients, which is tentatively attributed to its multiple targets. It is considered a potential replacement for poorly tolerated components of multidrug-resistant TB regimens. To prioritize SQ109-containing combinations with the best potential for cure and treatment shortening, one must understand its contribution against different bacterial populations in pulmonary lesions. Here, we have characterized the pharmacokinetics of SQ109 in the rabbit model of active TB and its penetration at the sites of disease-lung tissue, cellular and necrotic lesions, and caseum. A two-compartment model with first-order absorption and

elimination described the plasma pharmacokinetics. At the human-equivalent dose, parameter estimates fell within the ranges published for preclinical species. Tissue concentrations were modeled using an "effect" compartment, showing high accumulation in lung and cellular lesion areas with penetration coefficients in excess of 1,000 and lower passive diffusion in caseum after 7 daily doses. These results, together with the hydrophobic nature and high nonspecific caseum binding of SQ109, suggest that multiweek dosing would be required to reach steady state in caseum and poorly vascularized compartments, similar to bedaquiline. Linking lesion pharmacokinetics to SQ109 potency in assays against replicating, nonreplicating, and intracellular M. tuberculosis showed SQ109 concentrations markedly above pharmacokinetic-pharmacodynamic targets in lung and cellular lesions throughout the dosing interval.

DOI: 10.1128/AAC.00024-21
PMID: 34228540

29. **Whole-genome analysis of drug-resistant Mycobacterium tuberculosis reveals novel mutations associated with fluoroquinolone resistance.**

Int J Antimicrob Agents. 2021 Sep;58(3):106385. doi: 10.1016/j.ijantimicag.2021.106385. Epub 2021 Jun 20.

Chaiyachat P(1), Chaiprasert A(2), Nonghanphithak D(1), Smithtikarn S(3), Kamolwat P(3), Pungrassami P(3), Reechaipichitkul W(4), Ong RT(5), Teo YY(6), Faksri K(7).

Multidrug-resistant and extensively drug-resistant tuberculosis (M/XDR-TB) remains a global public-health challenge. Known mutations in quinolone resistance-determination regions cannot fully explain phenotypic fluoroquinolone (FQ) resistance in Mycobacterium tuberculosis (Mtb). The aim of this study was to look for novel mutations in Mtb associated with resistance to FQ drugs using whole-genome sequencing analysis. Whole-genome sequences of 659 Mtb strains, including 214 with phenotypic FQ resistance and 445 pan-susceptible isolates, were explored for mutations associated with FQ resistance overall and with resistance to individual FQ drugs (ofloxacin, levofloxacin, moxifloxacin and gatifloxacin). Three novel genes (recC, Rv2005c and PPE59) associated with FQ resistance were identified ($P < 0.00001$ based on screening analysis and absence of relevant mutations in a pan-susceptible validation set of 360 strains). Nine novel single nucleotide polymorphisms (SNPs), including in gyrB (G5383A and G6773A), gyrA (G7892A), recC (G725900C and G726857T/C), Rv2005c (C2251373G, G2251420C and C2251725T) and PPE59 (C3847269T), were used for diagnostic performance analysis. Enhancing the known SNP set with five of these novel SNPs, including gyrA [G7892A (Leu247Leu)], recC [G725900C (Leu893Leu) and G726857T/C

(Arg484Arg)], Rv2005c [G2251420C (Pro205Arg)] and PPE59 [C3847269T (Asn35Asn)] increased the sensitivity of detection of FQ-resistant Mtb from 83.2% (178/214) to 86.9% (186/214) while maintaining 100% specificity (360/360). No specific mutation associated with resistance to only a single drug (ofloxacin, levofloxacin, moxifloxacin or gatifloxacin) was found. In conclusion, this study reports possible additional mutations associated with FQ resistance in Mtb.

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DOI: 10.1016/j.ijantimicag.2021.106385
PMID: 34161790

30. **Compatibility of a novel filter paper-based bio-safe sputum transport kit with line probe assay for diagnosing drug-resistant tuberculosis: a single-site evaluation study.**

ERJ Open Res. 2021 Aug 2;7(3):00137-2021. doi: 10.1183/23120541.00137-2021. eCollection 2021 Jul.

Anthwal D(1)(2), Gupta RK(1)(2), Singhal R(3), Bhalla M(3), Verma AK(3), Khayyam KU(3), Myneedu VP(3), Sarin R(3), Gupta A(4), Gupta NK(4), Singh M(5), Sivaswami Tyagi J(2)(6), Haldar S(1)(2).

BACKGROUND: Near-patient access to appropriate tests is a major obstacle for the efficient diagnosis of tuberculosis (TB) and associated drug resistance.
METHODS: We recently developed the "TB Concentration & Transport" kit for bio-safe, ambient-temperature transportation of dried sputum on Trans-Filter, and the "TB DNA Extraction" kit for DNA extraction from Trans-Filter for determining drug resistance by DNA sequencing. In the present study, we evaluated the compatibility of Kit-extracted DNA with Hain's line probe assays (LPAs), which are endorsed by National TB programmes for the detection of drug resistance in sputum collected from presumptive multidrug-resistant TB patients (n=207).
RESULTS: Trans-Filter-extracted DNA was seamlessly integrated with the LPA protocol (Kit-LPA). The sensitivity of Kit-LPA for determining drug resistance was 83.3% for rifampicin (95% CI 52-98%), 77.7% for isoniazid (95% CI 52-94%), 85.7% for fluoroquinolones (95% CI 42-100%) and 66.6% for aminoglycosides (95% CI 9-99%), with a specificity range of 93.7% (95% CI 87-97) to 99.1% (95% CI 95-100) using phenotypic drug susceptibility testing (DST) as a reference standard. A high degree of concordance was noted between results obtained from Kit-LPA and LPA (99% to 100% (κ value: 0.83-1.0)).
CONCLUSIONS: This study demonstrates successful integration of our developed

kits with LPA. The adoption of these kits across Designated Microscopy Centres in India can potentially overcome the existing challenge of transporting infectious sputum at controlled temperature to centralised testing laboratories and can provide rapid near-patient cost-effective "Universal DST" services to TB subjects residing in remote areas.

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DOI: 10.1183/23120541.00137-2021
PMCID: PMC8326685
PMID: 34350282

31. **Detection of Pyrazinamide Heteroresistance in Mycobacterium tuberculosis.**

Antimicrob Agents Chemother. 2021 Aug 17;65(9):e0072021. doi: 10.1128/AAC.00720-21. Epub 2021 Aug 17.

Werngren J(1), Mansjö M(1), Glader M(1), Hoffner S(2), Davies Forsman L(3)(4).

Heteroresistance is defined as the coexistence of both susceptible and resistant bacteria in a bacterial population. Previously published data show that it may occur in 9 to 57% of Mycobacterium tuberculosis isolates for various drugs. Pyrazinamide (PZA) is an important first-line drug used for treatment of both drug-susceptible and PZA-susceptible multidrug-resistant TB. Clinical PZA resistance is defined as a proportion of resistant bacteria in the isolate exceeding 10%, when the drug is no longer considered clinically effective. The ability of traditional drug susceptibility testing techniques to detect PZA heteroresistance has not yet been evaluated. The aim of this study was to compare the capacity of Bactec MGIT 960, Wayne's test, and whole-genome sequencing (WGS) to detect PZA-resistant subpopulations in bacterial suspensions prepared with different proportions of mutant strains. Both Bactec MGIT 960 and WGS were able to detect the critical level of 10% PZA heteroresistance, whereas Wayne's test failed to do so, with the latter falsely reporting highly resistant samples as PZA susceptible. Failure to detect drug-resistant subpopulations may lead to inadvertently weak treatment regimens if ineffective drugs are included, with the risk of treatment failure with the selective growth of resistant subpopulations. We need clinical awareness of heteroresistance as well as evaluation of new diagnostic tools for their capacity to detect heteroresistance in TB.

DOI: 10.1128/AAC.00720-21
PMID: 34181476

32. **Post tuberculosis radiological sequelae in patients treated for pulmonary and pleural tuberculosis at a tertiary center in Pakistan.**

Monaldi Arch Chest Dis. 2021 Aug 2. doi: 10.4081/monaldi.2021.1814. Online ahead of print.

Zubair SM(1), Ali MG(2), Irfan M(3).

Treating tuberculosis (TB) is not the end of the disease because of the wide spectrum of post TB sequelae associated with the disease. There is insufficient data on post TB radiological sequelae. The aim of this study is to evaluate the post TB radiological sequelae on chest x-rays in patients who had completed the treatment for pulmonary and pleural TB at a tertiary care hospital of a high TB burden country. This is a retrospective cross-sectional study conducted on patients treated for pulmonary and pleural TB. Adult patients (18 years or above) with a clinical or microbiological diagnosis of pulmonary or pleural TB were included. Patients were classified on the basis of site of TB into pulmonary and pleural TB. Post-treatment radiological sequelae on chest x-ray were evaluated and divided into three main types i.e. fibrosis, bronchiectasis and pleural thickening. During the study period a total of 321 patients were included with a mean age of 44(SD±19) years. Only 17.13% (n=55) patients had normal chest x-rays at the end of treatment and 82.87% (n=266) patients had post-TB radiological sequelae with fibrosis being the most common followed by pleural thickening. The post TB radiological sequelae were high in patients who had diabetes mellitus (78.94%), AFB smear-positive (90.19%), AFB culture-positive (89.84%), Xpert MTB/Rif positive (88.40%) and with drug-resistant TB (100%). As a clinician, one should be aware of all the post TB sequelae so that early diagnosis and management can be facilitated.

DOI: 10.4081/monaldi.2021.1814
PMID: 34340298

33. **Resurgence of tuberculosis amid COVID-19 in Peru: Associated risk factors and recommendations.**

Int J Health Plann Manage. 2021 Jul 27. doi: 10.1002/hpm.3291. Online ahead of print.

Khan FMA(1), Kazmi Z(2), Hasan MM(3)(4), Dos Santos Costa AC(5), Ahmad S(6), Essar MY(7).

Peru is one of the countries with the highest incidence of tuberculosis and

multidrug-resistant tuberculosis in the world. Although public health measures adopted in the country have improved the care, diagnosis and management of patients with tuberculosis, there are still failures in the control of the disease in the country, especially of multidrug-resistant tuberculosis and among the prison population or people living with HIV. The COVID-19 pandemic has added a great burden to the Peruvian public health system, negatively impacting tuberculosis-focused health programs due to the diversion of resources to control the pandemic. Consequently, combat measures, epidemiological surveillance of tuberculosis cases were affected, and data point to an increase in the number of cases, especially of multidrug-resistant tuberculosis, and to the underdiagnosis of the disease. To deal with this problem and avoid a future catastrophe for the country's health system, multidisciplinary measures involving the population, health professionals and government bodies are needed. It is essential that education, diagnosis, contact screening and treatment programs are prioritised and given greater financial support. Furthermore, it is necessary to raise awareness in the population about the need for isolation and maintenance of treatment, especially among the most vulnerable populations.

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DOI: 10.1002/hpm.3291
PMID: 34318523

34. **Tuberculosis care cascade in Zambia - identifying the gaps in order to improve outcomes: a population-based analysis.**

BMJ Open. 2021 Aug 10;11(8):e044867. doi: 10.1136/bmjopen-2020-044867.

Lungu P(#)(1)(2), Kerkhoff AD(#)(3), Kasapo CC(4), Mzyece J(4), Nyimbili S(4), Chimzizi R(4), Silumesii A(5), Kagujje M(6), Subbaraman R(7), Muyoyeta M(6), Malama K(8).

OBJECTIVE: Tuberculosis (TB) remains a leading cause of morbidity and mortality in Zambia, especially for people living with HIV (PLHIV). We undertook a care cascade analysis to quantify gaps in care and align programme improvement measures with areas of need.
DESIGN: Retrospective, population-based analysis.
SETTING: We derived national-level estimates for each step of the TB care cascade in Zambia. Estimates were informed by WHO incidence estimates, nationally aggregated laboratory and notification registers, and individual-level programme data from four provinces.
PARTICIPANTS: Participants included all individuals with active TB disease in Zambia in 2018. We characterised the overall TB cascade and disaggregated by

drug susceptibility results and HIV status.
RESULTS: In 2018, the total burden of TB in Zambia was estimated to be 72 495 (range, 40 495-111 495) cases. Of these, 43 387 (59.8%) accessed TB testing, 40 176 (55.4%) were diagnosed with TB, 36 431 (50.3%) were started on treatment and 32 700 (45.1%) completed treatment. Among all persons with TB lost at any step along the care cascade (n=39 795), 29 108 (73.1%) were lost prior to accessing diagnostic services, 3211 (8.1%) prior to diagnosis, 3745 (9.4%) prior to initiating treatment and 3731 (9.4%) prior to treatment completion. PLHIV were less likely than HIV-negative individuals to successfully complete the care cascade (42.8% vs 50.2%, p<0.001). Among those with rifampicin-resistant TB, there was substantial attrition at each step of the cascade and only 22.8% were estimated to have successfully completed treatment.
CONCLUSIONS: Losses throughout the care cascade resulted in a large proportion of individuals with TB not completing treatment. Ongoing health systems strengthening and patient-centred engagement strategies are needed at every step of the care cascade; however, scale-up of active case finding strategies is particularly critical to ensure individuals with TB in the population reach initial stages of care. Additionally, a renewed focus on PLHIV and individuals with drug-resistant TB is urgently needed to improve TB-related outcomes in Zambia.

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DOI: 10.1136/bmjopen-2020-044867
PMID: 34376439 [Indexed for MEDLINE]

35. **Implementation of whole genome sequencing for tuberculosis diagnostics in a low-middle income, high MDR-TB burden country.**

Sci Rep. 2021 Jul 28;11(1):15333. doi: 10.1038/s41598-021-94297-z.

Vogel M(#)(1), Utpatel C(#)(2)(3), Corbett C(#)(1), Kohl TA(#)(2)(3), Iskakova A(#)(4), Ahmedov S(5), Antonenka U(1), Dreyer V(2)(3), Ibrahimova A(6), Kamarli C(7), Kosimova D(6), Mohr V(2)(3), Sahalchyk E(1), Sydykova M(4), Umetalieva N(1), Kadyrov A(8), Kalmambetova G(4), Niemann S(2)(3), Hoffmann H(9)(10).

Whole genome sequencing (WGS) is revolutionary for diagnostics of TB and its mutations associated with drug-resistances, but its uptake in low- and middle-income countries is hindered by concerns of implementation feasibility. Here, we provide a proof of concept for its successful implementation in such a setting. WGS was implemented in the Kyrgyz Republic. We estimated needs of up to 55 TB-WGS per week and chose the MiSeq platform (Illumina, USA) because of its

capacity of up to 60 TB-WGS per week. The project's timeline was completed in 93-weeks. Costs of large equipment and accompanying costs were 222,065 USD and 8462 USD, respectively. The first 174 WGS costed 277 USD per sequence, but this was skewed by training inefficiencies. Based on real prices and presuming optimal utilization of WGS capacities, WGS costs could drop to 167 and 141 USD per WGS using MiSeq Reagent Kits v2 (500-cycles) and v3 (600-cycles), respectively. Five trainings were required to prepare the staff for autonomous WGS which cost 48,250 USD. External assessment confirmed excellent performance of WGS by the Kyrgyz laboratory in an interlaboratory comparison of 30 M. tuberculosis genomes showing complete agreeance of results.

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DOI: 10.1038/s41598-021-94297-z
PMCID: PMC8319420
PMID: 34321545

36. **Expression profiling of TRIM gene family reveals potential diagnostic biomarkers for rifampicin-resistant tuberculosis.**

Microb Pathog. 2021 Aug;157:104916. doi: 10.1016/j.micpath.2021.104916. Epub 2021 May 15.

Liu S(1), Sun Y(2), Yang R(3), Ren W(4), Li C(5), Tang S(6).

The epidemic of pulmonary tuberculosis (TB), especially rifampin-resistant tuberculosis (RR-TB) presents a major challenge for TB control today. However, there is a lack of reliable and specific biomarkers for the early diagnosis of RR-TB. We utilized reverse transcription-quantitative polymerase chain reaction (RT-qPCR) to profile the transcript levels of 72 tripartite motif (TRIM) genes from a discovery cohort of 10 drug-sensitive tuberculosis (DS-TB) patients, 10 RR-TB patients, and 10 healthy controls (HCs). A total of 35 differentially expressed genes (DEGs) were screened out, all of which were down-regulated. The bio functions and pathways of these DEGs were enriched in protein ubiquitination, regulation of the viral process, Interferon signaling, and innate immune response, etc. A protein-protein interaction network (PPI) was constructed and analyzed using STRING and Cytoscape. Twelve TRIM genes were identified as hub genes, and seven (TRIM1, 9, 21, 32, 33, 56, 66) of them were verified by RT-qPCR in a validation cohort of 95 subjects. Moreover, we established the RR-TB decision tree models based on the 7 biomarkers. The receiver operating characteristic (ROC) analyses showed that the models exhibited the areas under the curve (AUC) values of 0.878 and 0.868 in discriminating RR-TB from HCs and DS-TB, respectively. Our study proposes

potential biomarkers for RR-TB diagnosis, and also provides a new experimental basis to understand the pathogenesis of RR-TB.

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DOI: 10.1016/j.micpath.2021.104916
PMID: 34000303 [Indexed for MEDLINE]

37. **Latent tuberculosis: interaction of virulence factors in Mycobacterium tuberculosis.**

Mol Biol Rep. 2021 Aug;48(8):6181-6196. doi: 10.1007/s11033-021-06611-7. Epub 2021 Aug 5.

Sundararajan S(1), Muniyan R(2).

Tuberculosis (TB) remains a prominent health concern worldwide. Besides extensive research and vaccinations available, attempts to control the pandemic are cumbersome due to the complex physiology of Mycobacterium tuberculosis (Mtb). Alongside the emergence of drug-resistant TB, latent TB has worsened the condition. The tubercle bacilli are unusually behaved and successful with its strategies to modulate genes to evade host immune system and persist within macrophages. Under latent/unfavorable conditions, Mtb conceals itself from immune system and modulates its genes. Among many intracellular modulated genes, important are those involved in cell entry, fatty acid degradation, mycolic acid synthesis, phagosome acidification inhibition, inhibition of phagosome-lysosome complex and chaperon protein modulation. Though the study on these genes date back to early times of TB, an insight on their inter-relation within and to newly evolved genes are still required. This review focuses on the findings and discussions on these genes, possible mechanism, credibility as target for novel drugs and repurposed drugs and their interaction that enables Mtb in survival, pathogenesis, resistance and latency.

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DOI: 10.1007/s11033-021-06611-7
PMID: 34351540

38. **Laboratory evolution of Mycobacterium on agar plates for analysis of resistance acquisition and drug sensitivity profiles.**

Sci Rep. 2021 Jul 23;11(1):15136. doi: 10.1038/s41598-021-94645-z.

Maeda T(1)(2), Kawada M(3), Sakata N(3), Kotani H(3), Furusawa C(3)(4).

Drug-resistant tuberculosis (TB) is a growing public health problem. There is an urgent need for information regarding cross-resistance and collateral sensitivity relationships among drugs and the genetic determinants of anti-TB drug resistance for developing strategies to suppress the emergence of drug-resistant pathogens. To identify mutations that confer resistance to anti-TB drugs in Mycobacterium species, we performed the laboratory evolution of nonpathogenic Mycobacterium smegmatis, which is closely related to Mycobacterium tuberculosis, against ten anti-TB drugs. Next, we performed whole-genome sequencing and quantified the resistance profiles of each drug-resistant strain against 24 drugs. We identified the genes with novel meropenem (MP) and linezolid (LZD) resistance-conferring mutation, which also have orthologs, in M. tuberculosis H37Rv. Among the 240 possible drug combinations, we identified 24 pairs that confer cross-resistance and 18 pairs that confer collateral sensitivity. The acquisition of bedaquiline or linezolid resistance resulted in collateral sensitivity to several drugs, while the acquisition of MP resistance led to multidrug resistance. The MP-evolved strains showed cross-resistance to rifampicin and clarithromycin owing to the acquisition of a mutation in the intergenic region of the Rv2864c ortholog, which encodes a penicillin-binding protein, at an early stage. These results provide a new insight to tackle drug-resistant TB.

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DOI: 10.1038/s41598-021-94645-z
PMCID: PMC8302736
PMID: 34302035

39. **WNT6/ACC2-induced storage of triacylglycerols in macrophages is exploited by Mycobacterium tuberculosis.**

J Clin Invest. 2021 Aug 16;131(16):e141833. doi: 10.1172/JCI141833.

Brandenburg J(1)(2), Marwitz S(3)(4), Tazoll SC(1), Waldow F(2)(5), Kalsdorf B(2)(6), Vierbuchen T(7), Scholzen T(8), Gross A(1), Goldenbaum S(1), Hölscher A(9), Hein M(8), Linnemann L(10), Reimann M(6), Kispert A(11), Leitges M(12), Rupp J(2)(13), Lange C(2)(6)(14)(15), Niemann S(2)(16), Behrends J(8), Goldmann T(3)(4), Heine H(7), Schaible UE(2)(10), Hölscher C(2)(9), Schwudke D(2)(4)(5), Reiling N(1)(2).

In view of emerging drug-resistant tuberculosis (TB), host-directed adjunct

therapies are urgently needed to improve treatment outcomes with currently available anti-TB therapies. One approach is to interfere with the formation of lipid-laden "foamy" macrophages in the host, as they provide a nutrient-rich host cell environment for Mycobacterium tuberculosis (Mtb). Here, we provide evidence that Wnt family member 6 (WNT6), a ligand of the evolutionarily conserved Wingless/Integrase 1 (WNT) signaling pathway, promotes foam cell formation by regulating key lipid metabolic genes including acetyl-CoA carboxylase 2 (ACC2) during pulmonary TB. Using genetic and pharmacological approaches, we demonstrated that lack of functional WNT6 or ACC2 significantly reduced intracellular triacylglycerol (TAG) levels and Mtb survival in macrophages. Moreover, treatment of Mtb-infected mice with a combination of a pharmacological ACC2 inhibitor and the anti-TB drug isoniazid (INH) reduced lung TAG and cytokine levels, as well as lung weights, compared with treatment with INH alone. This combination also reduced Mtb bacterial numbers and the size of mononuclear cell infiltrates in livers of infected mice. In summary, our findings demonstrate that Mtb exploits WNT6/ACC2-induced storage of TAGs in macrophages to facilitate its intracellular survival, a finding that opens new perspectives for host-directed adjunctive treatment of pulmonary TB.

DOI: 10.1172/JCI141833
PMCID: PMC8363280
PMID: 34255743

40. **Twenty-four-week interim outcomes of bedaquiline-containing regimens in treatment of adolescents with rifampicin-resistant tuberculosis: A retrospective cohort study in China.**

J Paediatr Child Health. 2021 Jul 29. doi: 10.1111/jpc.15672. Online ahead of print.

Wu HY(1), Tian Y(1), Wang XD(1), Sun JS(2), Fan LC(1), Chen MX(1), Li R(1), Chen Y(1).

AIM: To evaluate the 24-week interim outcomes of bedaquiline-containing regimens in the treatment of adolescents with rifampicin-resistant tuberculosis (RR-TB) in China.
METHODS: Adolescents with RR-TB from two hospitals were included in this retrospective study. All patients received the longer regimen containing bedaquiline. Sputum culture, chest computed tomography, blood tests and electrocardiography were performed regularly, and the outcomes after 24 weeks of treatment were reported.
RESULTS: Four male and six female adolescents aged 11 to 17 years old were included. Among them, four (40.0%), four (40.0%) and two (20.0%) were confirmed

to have RR-TB, multidrug-resistant TB and extensively drug-resistant TB, respectively. The most common companion drugs included linezolid (100.0%), cycloserine (90.0%), pyrazinamide (80.0%), moxifloxacin (50.0%) and levofloxacin (40.0%). Culture conversion rates of 80.0%, 100.0% and 100.0% were observed at weeks 2, 4 and 24, respectively. The mean maximum drug concentration of bedaquiline at weeks 2, 12 and 24 was 3.29 ± 0.66, 1.78 ± 0.81 and 1.93 ± 0.74 μg/mL, respectively. Six adverse events including leukopenia (50.0%), Fridericia-corrected QT (QTcF) interval prolongation (16.7%), anaemia (16.7%) and peripheral neuropathy (16.7%) were observed in five (50.0%) patients. No patient discontinued bedaquiline owing to QTcF interval prolongation. Meanwhile, no deaths, reversions or serious adverse events were reported during 24 weeks of treatment.
CONCLUSION: A longer regimen containing bedaquiline was effective and well tolerated in Chinese adolescents with RR-TB. The combination of bedaquiline and linezolid may be a favourable choice for this population.

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DOI: 10.1111/jpc.15672
PMID: 34323328

41. **Treatment Outcomes of Patients with Multidrug-Resistant Tuberculosis: Concern to Bedaquiline.**

Tuberc Respir Dis (Seoul). 2021 Aug 3. doi: 10.4046/trd.2021.0115. Online ahead of print.

We highly appreciated a study by Kang et al [1], who reported successful treatment outcomes and a lower case of lost follow-up after implementing the public-private mix period. The data were collected retrospectively over ten years. As we know, MDR-TB is still a complicated problem worldwide with a high level of treatment failure and mortality, including in Indonesia due to poor adherence and several adverse effects of drugs. Kang et al, also reported that MDR-TB patients with age more than 65 years old, a low body mass index, history of TB treatment, bilateral lung lesion, and pre or extensively drug-resistant TB (XDR-TB) were significantly associated with a treatment failure. Interestingly, the administration of bedaquiline or delamanide over one month was significantly associated with successful treatment (OR 5.939, CI95% 1.680- 20.991, p-value < 0.05)[1]. In a large cohort by Franke et al [2], 63% of MDR-TB patients using bedaquiline, delamanide, or both experienced culture conversion within six months after initiation of these drugs. Patients with HIV co-infection, high initially smear sputum, and cavitary lung disease had a lower conversion rate than those without these risks. In our country, Indonesia, either bedaquiline or delamanid was used for six months if patients

were intolerant, contraindicated, or resistant to a fluoroquinolone or second-line injectable antituberculosis drugs. Fortunately, bedaqualine has been listed in the national program as a part of the MDR-TB therapy in Indonesia, while belamanide was not [3]. However, the study about the efficacy and safety of bedaquiline for MDR-TB management in Indonesian was very limited. Although bedaquiline is well-tolerated, we should fully consider before administering it. The serious adverse effect of this drug, the Frederica-corrected (QTcF) prolongation, should be closely monitored by the pulmonologist and pharmacist [4]. In Indonesia, a study by Soeroto et al [5], reported that out of 492 MDR-TB patients, fifty percent of them had successful treatment. Culture conversion of sputum less than two months was significantly 2.79 more likely to successfully treat MDR-TB. At the same time, chronic kidney disease, HIV, and cavitary lesion were risk factors with more prolonged treatment. Unfortunately, bedaquiline was not reported in that study. Although bedaquiline or belanamide has a beneficial effect in treating MDR-TB patients, other factors that may inhibit sputum conversion or prolong the duration of therapy should be considered with supervising the side effects periodically.

Putra ON(1), Yuniar N H A(1).

DOI: 10.4046/trd.2021.0115
PMID: 34343423

42. **The Mur Enzymes Chink in the Armour of Mycobacterium tuberculosis cell wall.**

Eur J Med Chem. 2021 Oct 15;222:113568. doi: 10.1016/j.ejmech.2021.113568. Epub 2021 Jun 2.

Shinde Y(1), Ahmad I(1), Surana S(1), Patel H(2).

TUBERCULOSIS: (TB) transmitted by Mycobacterium tuberculosis (Mtb) is one of the top 10 causes of death globally. Currently, the widespread occurrence of resistance toward Mtb strains is becoming a significant concern to public health. This scenario exaggerated the need for the discovery of novel targets and their inhibitors. Targeting the "Mtb cell wall peptidoglycan synthesis" is an attractive strategy to overcome drug resistance. Mur enzymes (MurA-MurF) play essential roles in the peptidoglycan synthesis by catalyzing the ligation of key amino acid residues to the stem peptide. These enzymes are unique and confined to the eubacteria and are absent in humans, representing potential targets for anti-tubercular drug discovery. Mtb Mur ligases with the same catalytic mechanism share conserved amino acid regions and structural features that can conceivably exploit for the designing of the inhibitors, which can simultaneously target more than one isoforms (MurC-MurF) of the enzyme. In light of these findings in the current review, we have discussed the recent advances in medicinal chemistry of Mtb Mur enzymes (MurA-MurF) and their inhibitors,

offering attractive multi-targeted strategies to combat the problem of drug-resistant in M. tuberculosis.

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DOI: 10.1016/j.ejmech.2021.113568
PMID: 34118719

43. **Development of a nomogram for predicting treatment default under facility-based directly observed therapy short-course in a region with a high tuberculosis burden.**

Ther Adv Infect Dis. 2021 Jul 29;8:20499361211034066. doi: 10.1177/20499361211034066. eCollection 2021 Jan-Dec.

Wang S(1).

BACKGROUND: Poor adherence to tuberculosis (TB) treatment is a substantial barrier to global TB control. The aim of this study was to construct a nomogram for predicting the probability of TB treatment default.
METHODS: A total of 1185 TB patients who had received treatment between 2010 and 2011 in Peru were analyzed in this study. Patient demographics, social, and medical information were recorded. Predictors were selected by least absolute shrinkage and selection operator (LASSO) regression analysis, and a nomogram for predicting TB treatment default was constructed by using multivariable logistic regression analysis. Bootstrapping method was applied for internal validation. Calibration and clinical utility of the nomogram was also evaluated.
RESULTS: The incidence of TB treatment default among the study patients was 11.6% (138/1185). Six predictors (secondary education status, alcohol use, illegal drug use, body mass index, multidrug-resistant tuberculosis, and human immunodeficiency virus serostatus) were selected through the LASSO regression analysis. A nomogram was developed based on the six predictors and it yielded an area under the curve (AUC) value of 0.797 [95% confidence interval (CI), 0.755-0.839]. In the internal validation, the AUC achieved 0.805 (95% CI, 0.759-0.844). Additionally, the nomogram was well-calibrated, and it showed clinical utility in decision curve analysis.
CONCLUSION: A nomogram was constructed that incorporates six characteristics of the TB patients, which provides a good reference for predicting TB treatment default.

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DOI: 10.1177/20499361211034066

PMCID: PMC8330448
PMID: 34377465

44. **Natural products from Brazilian biodiversity identified as potential inhibitors of PknA and PknB of M. tuberculosis using molecular modeling tools.**

Comput Biol Med. 2021 Jul 28;136:104694. doi: 10.1016/j.compbiomed.2021.104694. Online ahead of print.

Antunes SS(1), Won-Held Rabelo V(2), Romeiro NC(3).

Mycobacterium tuberculosis was discovered in 1882 by Robert Koch but, since its discovery, the tuberculosis (TB) epidemic has endured, being one of the top 10 causes of death worldwide. Drug-resistant TB continues to be a public health threat and bioactive compounds with a new mode of action (MoA) are needed to overcome this. Since natural products are described as important sources for the development of new drugs, the objective of this work was to identify potential ligands from Brazilian natural products (NPs) for M. tuberculosis targets using molecular modeling tools. Using chemogenomics we identified the Serine/Threonine Protein Kinase PknB as a putative target for 13 NPs from a database from Brazilian biodiversity (NuBBE). Literature data supported further investigation of NuBBE105, NuBBE598, NuBBE936, NuBBE964, NuBBE1045, and NuBBE1180 by molecular docking and dynamics. Key interactions were observed with PknB and simulations confirmed stability and favorable binding energies. Considering structural similarity with PknB, we further explored binding of the NPs to PknA, critical for M. tuberculosis survival, and all of them resembled important interactions with the enzyme, showing stable and favorable binding energies, whilst van der Waals interactions seem to play a key role for binding to PknA and PknB. NuBBE936 and NuBBE1180 have already had their antimycobacterial activity reported and our results can provide a basis for their MoA. Finally, the other NPs which have not been tested against M. tuberculosis deserve further investigation, aiming at the discovery of antimycobacterial drug candidates with innovative MoA.

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DOI: 10.1016/j.compbiomed.2021.104694
PMID: 34365277

45. **Rv0684/fusA1, an Essential Gene, Is the Target of Fusidic Acid and Its Derivatives in Mycobacterium tuberculosis.**

ACS Infect Dis. 2021 Aug 13;7(8):2437-2444. doi: 10.1021/acsinfecdis.1c00195. Epub 2021 Jul 1.

Singh V(1)(2)(3), Dziwornu GA(2)(4), Mabhula A(2)(3), Chibale K(1)(2)(3).

Tuberculosis (TB), caused by Mycobacterium tuberculosis, is a major global health concern given the increase in multiple forms of drug-resistant TB. This underscores the importance of a continuous pipeline of new anti-TB agents. Drug repurposing has shown promise in expanding the therapeutic options for TB chemotherapy. Fusidic acid (FA), a natural product-derived antibiotic, is one such candidate for repurposing. The present study aimed to understand the mechanism of action of FA and its selected analogs in M. tuberculosis. By using chemical biology and genetics, we identified elongation factor G as the target of FA in M. tuberculosis. We showed essentiality of its encoding gene fusA1 in M. tuberculosis by demonstrating that the transcriptional silencing of fusA1 is bactericidal in vitro and in macrophages. Thus, this work validated a novel drug target FusA1 in M. tuberculosis.

DOI: 10.1021/acsinfecdis.1c00195
PMID: 34196521

46. **Intragenic Distribution of IS6110 in Clinical Mycobacterium tuberculosis Strains: Bioinformatic Evidence for Gene Disruption Leading to Underdiagnosed Antibiotic Resistance.**

Microbiol Spectr. 2021 Jul 21:e0001921. doi: 10.1128/Spectrum.00019-21. Online ahead of print.

Antoine R(1), Gaudin C(1), Hartkoorn RC(1).

Antibiotic resistance is a global challenge for tuberculosis control, and accelerating its diagnosis is critical for therapy decisions and controlling transmission. Genotype-based molecular diagnostics now play an increasing role in accelerating the detection of such antibiotic resistance, but their accuracy depends on the instructed detection of genetic variations. Genetic mobile elements such as IS6110 are established sources of genetic variation in Mycobacterium tuberculosis, but their implication in clinical antibiotic resistance has thus far been unclear. Here, we describe the discovery of an intragenic IS6110 insertion into Rv0678 that caused antibiotic resistance in an in vitro-selected M. tuberculosis isolate. The subsequent development of bioinformatics scripts allowed genome-wide analysis of intragenic IS6110 insertions causing gene disruptions in 6,426 clinical M. tuberculosis strains. This analysis identified 10,070 intragenic IS6110 insertions distributed among

333 different genes. Focusing on genes whose disruption leads to antibiotic resistance, 12 clinical isolates were identified with high confidence to be resistant to bedaquiline, clofazimine, pyrazinamide, ethionamide, and para-aminosalicylic acid because of an IS6110-mediated gene disruption event. A number of these IS6110-mediated resistant strains had identical genomic distributions of IS6110 elements and likely represent transmission events of a single resistant isolate. These data provide strong evidence that IS6110-mediated gene disruption is a clinically relevant mechanism of antibiotic resistance in M. tuberculosis that should be considered for molecular diagnostics. Concomitantly, this analysis provides a list of 333 IS6110-disrupted genes in clinical tuberculosis isolates that can be deemed nonessential for human infection. IMPORTANCE To help control the spread of drug-resistant tuberculosis and to guide treatment choices, it is important that rapid and accurate molecular diagnostic tools are used. Current molecular diagnostic tools detect the most common antibiotic-resistance-conferring mutations in the form of single nucleotide changes, small deletions, or insertions. Mobile genetic elements, named IS6110, are also known to move within the M. tuberculosis genome and cause significant genetic variations, although the role of this variation in clinical drug resistance remains unclear. In this work, we show that both in vitro and in data analyzed from 6,426 clinical M. tuberculosis strains, IS6110 elements are found that disrupt specific genes essential for the function of a number of pivotal antituberculosis drugs. By providing ample evidence of clinically relevant IS6110-mediated drug resistance, we believe that this shows that this form of genetic variation must not be overlooked in molecular diagnostics of drug resistance.

DOI: 10.1128/Spectrum.00019-21
PMID: 34287057

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

Clin Infect Dis. 2021 Aug 18:ciaa617. doi: 10.1093/cid/ciaa617. Online ahead of print.

Hamilton CD(1).

Multi-drug and extensively-drug-resistant (MDR and XDR) tuberculosis (TB) are life-threatening, contagious diseases. Patients who have these infections are challenging to study because of the heterogenous nature of their pathogens and varying host immunity. Though never tested in head-to-head clinical trials, successful treatment of MDR- or XDR-TB typically includes one of four injectable anti-TB agents. The article by Cegielski et al [1] in the current issue of CID concludes that we may have missed important differences in the drugs' effectiveness. The

individual patient dataset (IPD) the authors draw from is rigorously curated, and the analyses were performed according to accepted standards. Their conclusions are supported by the data presented. Most importantly, the findings are clinically meaningful, and are highly relevant to policy makers and guidelines-producers.
DOI: 10.1093/cid/ciaa617
PMID: 34407174

48. **Analytical performance of the Xpert MTB/XDR® assay for tuberculosis and expanded resistance detection.**

Diagn Microbiol Infect Dis. 2021 Sep;101(1):115397. doi: 10.1016/j.diagmicrobio.2021.115397. Epub 2021 Apr 20.

Georghiou SB(1), Penn-Nicholson A(1), de Vos M(1), Macé A(1), Syrmis MW(2), Jacob K(3), Mape A(3), Parmar H(4), Cao Y(4), Coulter C(3), Ruhwald M(1), Pandey SK(3), Schumacher SG(5), Denkinger CM(6).

In a manufacturer-independent laboratory validation study, the Xpert MTB/XDR® assay demonstrated equivalent limit of detection to Xpert MTB/RIF®, detected 100% of tested resistance mutations and showed some utility for resistance detection in strain mixtures. The Xpert MTB/XDR assay is a reliable, sensitive assay for tuberculosis and expanded resistance detection.

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DOI: 10.1016/j.diagmicrobio.2021.115397
PMID: 34130215

49. **Stepwise selection of mutation conferring fluroquinolone resistance: multisite MDR-TB cohort study.**

Eur J Clin Microbiol Infect Dis. 2021 Aug;40(8):1767-1771. doi: 10.1007/s10096-021-04187-5. Epub 2021 Feb 18.

Gao J(#)(1), Du J(#)(1), Shu W(#)(1), Liu Y(1), Wang Y(2), Xue Z(2), Li L(3), Pang Y(4).

In this study, we demonstrate that fluroquinolone (FQ) is at risk of acquired drug resistance after continuous exposure. The reduced susceptibility is observed in subsequent Mycobacterium tuberculosis isolates from patients without FQ exposure. The stepwise selection of mutation of increasing FQ resistance highlights the urgent need for monitoring FQ resistance in multidrug-resistant

tuberculosis patients throughout the entire treatment course.

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PMID: 33604720

50. **Identification of novel benzothiopyranones with ester and amide motifs derived from active metabolite as promising leads against Mycobacterium tuberculosis.**

Eur J Med Chem. 2021 Oct 15;222:113603. doi: 10.1016/j.ejmech.2021.113603. Epub 2021 Jun 5.

Li P(1), Wang B(2), Fu L(2), Guo K(3), Ma C(3), Wang B(3), Lin Z(1), Li G(4), Huang H(5), Lu Y(6).

We reported three distinct series of novel benzothiopyranones, derived from an active metabolite (M-1) of anti-TB agent 6b. These small molecules were evaluated for their biological activities against a range of Mycobacterium tuberculosis (M. tuberculosis) strains. Preliminary druggability evaluation demonstrated that M-1 showed good aqueous solubility and hepatocyte stability. Benzothiopyranones with acyl, sulfonyl and phosphoryl groups exhibited potent in vitro inhibitory activity against M. tuberculosis H37Rv and low cytotoxicity. In particular, compound 3d, containing a benzoate fragment, displayed marked metabolic stability and potent in vitro activity against drug-resistant tuberculosis clinical strains. Further druggability evaluation based on the identified compounds 3d, 4e and 5b is ongoing for the discovery of promising anti-TB agents.

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PMID: 34126456

51. **Mycobacterium enoyl acyl carrier protein reductase (InhA): A key target for antitubercular drug discovery.**

Bioorg Chem. 2021 Aug 8;115:105242. doi: 10.1016/j.bioorg.2021.105242. Online ahead of print.

Prasad MS(1), Bhole RP(2), Khedekar PB(3), Chikhale RV(4).

Enoyl acyl carrier protein reductase (InhA) is a key enzyme involved in fatty acid synthesis mainly mycolic acid biosynthesis that is a part of NADH dependent acyl carrier protein reductase family. The aim of the present literature is to underline the different scaffolds or enzyme inhibitors that inhibit mycolic acid biosynthesis mainly cell wall synthesis by inhibiting enzyme InhA. Various scaffolds were identified based on the screening technologies like high throughput screening, encoded library technology, fragment-based screening. The compounds studied include indirect inhibitors (Isoniazid, Ethionamide, Prothionamide) and direct inhibitors (Triclosan/Diphenyl ethers, Pyrrolidine Carboxamides, Pyrroles, Acetamides, Thiadiazoles, Triazoles) with better efficacy against drug resistance. Out of the several scaffolds studied, pyrrolidine carboxamides were found to be the best molecules targeting InhA having good bioavailability properties and better MIC. This review provides with a detailed information, analysis, structure activity relationship and useful insight on various scaffolds as InhA inhibitors.

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PMID: 34392175

52. **Binding profile of protein-ligand inhibitor complex and structure based design of new potent compounds via computer-aided virtual screening.**

J Clin Tuberc Other Mycobact Dis. 2021 Jun 26;24:100256. doi: 10.1016/j.jctube.2021.100256. eCollection 2021 Aug.

Shallangwa GA(1), Adeniji SE(1).

BACKGROUND: Mycobacterium tuberculosis protein target (DNA gyrase) is a type II topoisomerase target present in all bacteria. The enzyme comprises of two subunits A and B. DNA binding domain is located in the subunits A while the catalysis and cleavage of two DNA strands occur in the subunits A using ATP hydrolysis. This enzyme has been reported to emerge in extensively drug resistant tuberculosis. Therefore this research aimed to design new potent compounds against the target and establish the analysis of protein-ligand binding interaction between the target and novel quinoline analogues via the application of in silicovirtual screening to predict the inhibition binding affinities the analogues.
RESULT: The docking results revealed that compound ID 17 with efficient inhibition activity has a noticeable binding affinity of -18.8 kcal/mol. Hence compound 17 was designated as the reference template to designed novel fourteen

compounds with higher binding affinities as a promising compounds. CONCLUSION: Designed compound 17i, 17j and 17n with lead binding affinities among the designed compounds were observed with the most perceptible binding affinity which ranges from (-21.2 to -26.8) kcal/mol compared to low binding affinity (-5.8 kcal/mol) computed for ethambutol.

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PMCID: PMC8258700
PMID: 34307904

53. **A novel agar base medium for drug susceptibility testing of Mycobacterium tuberculosis isolates.**

Future Microbiol. 2021 Aug 13. doi: 10.2217/fmb-2021-0032. Online ahead of print.

Coban AY(1)(2)(3).

Aim: In this study, it was aimed to evaluate AYC.2.2 agar for susceptibility testing of Mycobacterium tuberculosis clinical isolates against first line drugs. Materials & methods: In the present study, 208 M. tuberculosis clinical isolates were tested on AYC.2.2 agar, which was previously validated for the first line drugs isoniazid, rifampicin, streptomycin and ethambutol. Results: Specificity, sensitivity, positive predictive value, negative predictive value and agreement for isoniazid-rifampicin-ethambutol-streptomycin were 100-100-97.2-99.3%, 94.8-94.8-79.3-94.3%, 100-100-82.1-98.03%, 97.03-98.03-96.7-98.08%, 98.07-98.5-94.7-98.07%, respectively. Conclusion: Results had shown that the newly developed AYC.2.2 agar promises as an alternative medium that can be used to perform susceptibility testing of M. tuberculosis isolates. However, further multicenter studies are needed to be used in routine mycobacteriology laboratories.

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