September Literature

1. Prevalence of extensively drug-resistant tuberculosis in a Chinese multidrug-resistant TB cohort after redefinition.

Antimicrob Resist Infect Control. 2021 Aug 26;10(1):126. doi: 10.1186/s13756-021-00995-8.

Yao C(#)(1), Guo H(#)(1), Li Q(#)(2), Zhang X(1), Shang Y(1), Li T(3), Wang Y(4), Xue Z(4), Wang L(1), Li L(1), Pang Y(5).

OBJECTIVES: Recently, the definition of extensively drug-resistant TB (XDR-TB) has been revised. In this study, we conducted a descriptive and retrospective study to determine the prevalence of XDR-TB in a Chinese multidrug-resistant TB (MDR-TB) cohort.
METHODS: Broth microdilution method was performed to determine in vitro susceptibilities of Mycobacterium tuberculosis (MTB) isolates to (FQs), bedaquiline (BDQ) and linezolid (LZD). The putative drug target genes conferring drug resistance were screened by DNA sequencing.
RESULTS: A total of 425 MDR-TB isolates were included from 13 pilots in China. LZD and BDQ resistance were noted in 30 (7.1%) and 10 (2.4%) isolates. On the basis of latest definitions, 114 (26.8%) were MDR-TB, 282 (66.4%) were pre-XDR-TB, and 29 (6.8%) were XDR-TB. Among 311 FQ-resistant isolates, 265 harbored genetic mutations within QRDRs. The most common mutations were observed at codon 94 of gyrA, accounting for 47.2% of FQ-resistant MTB isolates. Only mutations within the Rv0678 gene were found to confer BDQ resistance in our cohort, conferring 40.0% of BDQ resistance. For LZD resistance, 53.3% of LZD-resistant isolates carried genetic mutations in rplC or 23S rRNA. The most frequent mutation was Cys154Arg in the rplC gene. In addition, we recorded two MDR-TB patients with resistance to both BDQ and LZD, of which one patient experienced continuous positive culture of MTB despite inclusion of efficacious moxifloxacin.
CONCLUSION: Our results demonstrate that the low prevalence of XDR-TB holds great promise for MDR-TB treatment with WHO-endorsed regimens containing BDQ-LZD combination, whereas the high prevalence of FQ-resistance in MDR-TB patients warrants national attention.

DOI: 10.1186/s13756-021-00995-8
PMCID: PMC8393791
PMID: 34446095

2. Outcome of treatment of MDR-TB or drug-resistant patients treated with bedaquiline and delamanid: Results from a large global cohort.

Pulmonology. 2021 Sep-Oct;27(5):403-412. doi: 10.1016/j.pulmoe.2021.02.006. Epub 2021 Mar 19.

Koirala S(1), Borisov S(2), Danila E(3), Mariandyshev A(4), Shrestha B(5), Lukhele N(6), Dalcolmo M(7), Shakya SR(8), Miliauskas S(9), Kuksa L(10), Manga S(11), Aleksa A(12), Denholm JT(13), Khadka HB(14), Skrahina A(15), Diktanas S(16), Ferrarese M(17), Bruchfeld J(18), Koleva A(19), Piubello A(20), Koirala GS(21), Udwadia ZF(22), Palmero DJ(23), Munoz-Torrico M(24), Gc R(25), Gualano G(26), Grecu VI(27), Motta I(28), Papavasileiou A(29), Li Y(30), Hoefsloot W(31), Kunst H(32), Mazza-Stalder J(33), Payen MC(34), Akkerman OW(35), Bernal E(36), Manfrin V(37), Matteelli A(38), Mustafa Hamdan H(39), Nieto Marcos M(40), Cadiñanos Loidi J(41), Cebrian Gallardo JJ(42), Duarte R(43), Escobar Salinas N(44), Gomez Rosso R(45), Laniado-Laborín R(46), Martínez Robles E(47), Quirós Fernandez S(48), Rendon A(49), Solovic I(50), Tadolini M(51), Viggiani P(52), Belilovski E(2), Boeree MJ(31), Cai Q(53), Davidavičienė E(54), Forsman LD(18), De Los Rios J(55), Drakšienė J(16), Duga A(56), Elamin SE(39), Filippov A(2), Garcia A(23), Gaudiesiute I(9), Gavazova B(57), Gayoso R(7), Gruslys V(3), Jonsson J(58), Khimova E(4), Madonsela G(59), Magis-Escurra C(31), Marchese V(38), Matei M(60), Moschos C(29), Nakčerienė B(54), Nicod L(33), Palmieri F(26), Pontarelli A(61), Šmite A(10), Souleymane MB(20), Vescovo M(23), Zablockis R(3), Zhurkin D(15), Alffenaar JW(62), Caminero JA(63), Codecasa LR(17), García-García JM(64), Esposito S(65), Saderi L(66), Spanevello A(67), Visca D(67), Tiberi S(68), Pontali E(69), Centis R(70), D'Ambrosio L(71), van den Boom M(72), Sotgiu G(66), Migliori GB(73).

The World Health Organization (WHO) recommends countries introduce new anti-TB drugs in the treatment of multidrug-resistant tuberculosis. The aim of the study is to prospectively evaluate the effectiveness of bedaquiline (and/or delamanid)- containing regimens in a large cohort of consecutive TB patients treated globally. This observational, prospective study is based on data collected and provided by Global Tuberculosis Network (GTN) centres and analysed twice a year. All consecutive patients (including children/adolescents) treated with bedaquiline and/or delamanid were enrolled, and managed according to WHO and national guidelines. Overall, 52 centres from 29 countries/regions in all continents reported 883 patients as of January 31st 2021, 24/29 countries/regions providing data on 100% of their consecutive patients (10-80% in the remaining 5 countries). The drug-resistance pattern of the patients was severe (>30% with extensively drug-resistant -TB; median number of resistant drugs 5 (3-7) in the overall cohort and 6 (4-8) among patients with a final outcome). For the patients with a final outcome (477/883, 54.0%) the median (IQR) number of months of anti-TB treatment was 18 (13-23) (in days 553 (385-678)). The proportion of patients achieving sputum smear and culture conversion ranged from 93.4% and 92.8% respectively (whole cohort) to 89.3% and 88.8% respectively (patients with a final outcome), a median (IQR) time to sputum smear and culture conversion of 58 (30-90) days for the whole cohort and 60 (30-100) for patients with a final outcome and, respectively, of 55 (30-90) and 60 (30-90) days for culture conversion. Of

383 patients treated with bedaquiline but not delamanid, 284 (74.2%) achieved treatment success, while 25 (6.5%) died, 11 (2.9%) failed and 63 (16.5%) were lost to follow-up.

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PMID: 33753021

3. **Outcome of community-initiated treatment of drug-resistant tuberculosis patients in Lagos, Nigeria.**

Trans R Soc Trop Med Hyg. 2021 Sep 3;115(9):1061-1065. doi: 10.1093/trstmh/traa188.

Bakare AM(1), Udunze OC(1), Bamidele JO(2), Omoniyi A(3), Osman E(1), Daniel OJ(2).

BACKGROUND: With the improvement in the capacity to diagnose multidrug-resistant/rifampicin-resistant tuberculosis (MDR/RR-TB) patients due to the increased number of GeneXpert machines in Nigeria, the number of patients diagnosed surpassed the bed capacity at MDR-TB treatment centres. Community DR-TB treatment is an important option to improve access to care for MDR/RR-TB patients. However, few studies have determined the outcome of community management of MDR-TB patients, which this study aims to address.
METHODS: We conducted a retrospective study of MDR/RR-TB patients initiated on treatment in the community in Lagos, Nigeria, between 1 January 2015 and 31 December 2016. Data were retrieved from DR-TB treatment cards/registers. The treatment outcomes of these patients were assessed at the end of treatment and categorized according to national TB guidelines.
RESULTS: A total of 150 DR-TB patients commenced treatment during the study period. Adherence was 64.7%, with the majority of patients experiencing mild (56.5%) adverse drug events. Treatment was successful in 70% of patients. The only predictor of successful treatment was treatment adherence.
CONCLUSIONS: The study shows that community initiation of MDR-TB treatment is feasible and results in a high treatment success rate. Adherence counselling before and during treatment is essential for a favourable treatment outcome.

DOI: 10.1093/trstmh/traa188
PMCID: PMC8416778

PMID: 33427297

4. **Multidrug-resistant tuberculosis imported into low-incidence countries-a GeoSentinel analysis, 2008-2020.**

J Travel Med. 2021 Aug 27;28(6):taab069. doi: 10.1093/jtm/taab069.

Eimer J(1), Patimeteeporn C(2), Jensenius M(3), Gkrania-Klotsas E(4), Duvignaud A(5), Barnett ED(6), Hochberg NS(7), Chen LH(8), Trigo-Esteban E(9), Gertler M(10), Greenaway C(11), Grobusch MP(12)(13), Angelo KM(2), Hamer DH(7)(14), Caumes E(15)(16), Asgeirsson H(1)(17).

BACKGROUND: Early detection of imported multidrug-resistant tuberculosis (MDR-TB) is crucial, but knowledge gaps remain about migration- and travel-associated MDR-TB epidemiology. The aim was to describe epidemiologic characteristics among international travellers and migrants with MDR-TB.
METHODS: Clinician-determined and microbiologically confirmed MDR-TB diagnoses deemed to be related to travel or migration were extracted from GeoSentinel, a global surveillance network of travel and tropical medicine clinics, from January 2008 through December 2020. MDR-TB was defined as resistance to both isoniazid and rifampicin. Additional resistance to either a fluoroquinolone or a second-line injectable drug was categorized as pre-extensively drug-resistant (pre-XDR) TB, and as extensively drug-resistant (XDR) TB when resistance was detected for both. Sub-analyses were performed based on degree of resistance and country of origin.
RESULTS: Of 201 patients, 136 had MDR-TB (67.7%), 25 had XDR-TB (12.4%), 23 had pre-XDR TB (11.4%) and 17 had unspecified MDR- or XDR-TB (8.5%); 196 (97.5%) were immigrants, of which 92 (45.8%) originated from the former Soviet Union. The median interval from arrival to presentation was 154 days (interquartile range [IQR]: 10-751 days); 34.3% of patients presented within 1 month after immigration, 30.9% between 1 and 12 months and 34.9% after ≥1 year. Pre-XDR- and XDR-TB patients from the former Soviet Union other than Georgia presented earlier than those with MDR-TB (26 days [IQR: 8-522] vs. 369 days [IQR: 84-827]), while patients from Georgia presented very early, irrespective of the level of resistance (8 days [IQR: 2-18] vs. 2 days [IQR: 1-17]).
CONCLUSIONS: MDR-TB is uncommon in traditional travellers. Purposeful medical migration may partly explain differences in time to presentation among different groups. Public health resources are needed to better understand factors contributing to cross-border MDR-TB spread and to develop strategies to optimize care of TB-infected patients in their home countries before migration.

DOI: 10.1093/jtm/taab069
PMID: 33987682

5. **Undernutrition and Treatment Success in Drug-Resistant Tuberculosis in Uganda.**

Infect Drug Resist. 2021 Sep 9;14:3673-3681. doi: 10.2147/IDR.S332148.
eCollection 2021.

Baluku JB(1)(2), Namiiro S(2), Nabwana M(3), Muttamba W(2), Kirenga B(2).

BACKGROUND: Undernutrition is associated with unfavourable treatment outcomes among people with drug-resistant tuberculosis (DRTB). Factors influencing the treatment outcomes among undernourished people with DRTB are not well characterised. The aim of this study was to determine factors associated with treatment success among undernourished people with DRTB in Uganda.
METHODS: We analysed data from a retrospective cohort of people with DRTB from 16 treatment sites in Uganda. We included participants with a pre-treatment body mass index (BMI) of <18.5 kilograms/meters2 (kg/m2). Participants were categorised as having mild (BMI of 18.5-17 kg/m2), moderate (BMI of 16.9-16.0 kg/m2) or severe (BMI of <16.0 kg/m2) undernutrition. We performed logistic regression analysis to determine factors associated with treatment success.
RESULTS: Among 473 people with DRTB, 276 (58.4%) were undernourished (BMI < 18.5 Kg/m2) and were included in the study. Of these, 92 (33.3%) had mild, 69 (25.0%) had moderate and 115 (41.7%) had severe undernutrition. The overall treatment success rate (TSR) for the undernourished was 71.4% (n = 197). Although the TSR was similar among participants with mild (71.7%), moderate (78.3%) and severe (67.0%) undernutrition (p = 0.258), all treatment failure cases (n =6) were among participants with severe undernutrition (p = 0.010). Cigarette smoking (odds ratio (OR) = 0.19, 95% CI 0.07-0.47, p < 0.001), urban residence (OR = 0.31, 95% CI 0.14-0.70, p = 0.005) and moderate (OR = 0.14, 95% CI 0.06-0.35, p < 0.001) and severe anaemia (OR = 0.06, 95% CI 0.01-0.29, p = 0.001) were associated with lower odds of treatment success.
CONCLUSION: Most undernourished people with DRTB have severe undernutrition. Smoking and anaemia are modifiable factors which upon appropriate intervention could improve treatment success. The effect of urban residence on the TSR needs to be evaluated further.

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PMCID: PMC8437412

PMID: 34526787

6. **Whole genome sequencing of clinical samples reveals extensively drug resistant tuberculosis (XDR TB) strains from the Beijing lineage in Nigeria, West Africa.**

Sci Rep. 2021 Aug 30;11(1):17387. doi: 10.1038/s41598-021-96956-7.

Olawoye IB(1)(2), Uwanibe JN(1)(2), Kunle-Ope CN(3), Davies-Bolorunduro OF(3), Abiodun TA(3), Audu RA(3), Salako BL(3), Happi CT(4)(5).

Multi-drug (MDR) and extensively drug-resistant (XDR) tuberculosis (TB) continues to be a global public health problem especially in high TB burden countries like Nigeria. Many of these cases are undetected and go on to infect high risk individuals. Clinical samples from positive rifampicin resistant Xpert®MTB/Rif assay were subjected to direct whole genome sequencing and bioinformatics analysis to identify the full antibiotics resistance and lineage profile. We report two (2) XDR TB samples also belonging to the East-Asian/Beijing family of lineage 2 Mycobacterium tuberculosis complex from clinical samples in Nigeria. Our findings further reveal the presence of mutations that confer resistance to first-line drugs (rifampicin, isoniazid, ethambutol and pyrazanimide), second-line injectables (capreomycin, streptomycin, kanamycin and/or amikacin) and at least one of the fluoroquinolones (ofloxacin, moxifloxacin, levofloxacin and/or ciprofloxacin) in both samples. The genomic sequence data from this study not only provide the first evidence of XDR TB in Nigeria and West Africa, but also emphasize the importance of WGS in accurately detecting MDR and XDR TB, to ensure adequate and proper management treatment regimens for affected individuals. This will greatly aid in preventing the spread of drug resistance TB in high burden countries.

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PMCID: PMC8405707
PMID: 34462504

7. **Depression and its associated factors among people with multidrug-resistant tuberculosis in Myanmar.**

Trop Med Int Health. 2021 Sep;26(9):1117-1126. doi: 10.1111/tmi.13637. Epub 2021 Jun 24.

Theingi P(1)(2), Kamiya Y(2), Myat Moe M(1), Cho San C(1), Cox SE(2)(3)(4).

BACKGROUND: Depression is an important potential comorbidity in persons with tuberculosis (TB), yet data in many settings are scarce.
OBJECTIVE: To estimate the prevalence and risk factors of depression in persons with multidrug-resistant tuberculosis (MDR-TB) in Myanmar.
METHODS: A cross-sectional survey among MDR-TB participants at Aung San MDR-TB treatment centre in Yangon during routine clinic follow-up visits. Patients Health Questionnaire-9 (PHQ-9) in the local language was used to screen for depression and structured questionnaires conducted. Univariable and multivariable logistic regression models were performed to identify associations.
RESULTS: Three-hundred and twenty-nine participants were enrolled between 19th December 2019 and 31st January 2020; 33% (111/329) in the intensive treatment phase. The prevalence of depressive symptoms (PHQ-9 ≥ 10) was (34/329) 10.33%. Multivariable analysis indicated financial hardship as a result of MDR-TB symptoms/treatment (aOR = 2.63, 95%CI: 1.12-6.67), suffering ≥1 respiratory symptoms (aOR = 6.72, 95%CI: 2.41-18.76), high education level (aOR = 4.26, 95%CI: 1.70-10.70), reported diabetes (aOR = 3.05, 95%CI: 1.16-7.99) as associated with depressive symptoms, with weak evidence of an association in females (aOR = 2.09, 95%CI: 0.94-4.65).
CONCLUSION: Depressive symptoms are more common in those with comorbidities/TB symptoms. Further research is required to determine the effects of interventions to support persons with depressive symptoms identified using simple, standardised validated tools like PHQ-9.

DOI: 10.1111/tmi.13637
PMID: 34110669

8. **Quantifying transmission fitness costs of multi-drug resistant tuberculosis.**

Epidemics. 2021 Sep;36:100471. doi: 10.1016/j.epidem.2021.100471. Epub 2021 May 21.

Pečerska J(1), Kühnert D(2), Meehan CJ(3), Coscollá M(4), de Jong BC(5), Gagneux S(6), Stadler T(7).

As multi-drug resistant tuberculosis (MDR-TB) continues to spread, investigating the transmission potential of different drug-resistant strains becomes an ever more pressing topic in public health. While phylogenetic and transmission tree inferences provide valuable insight into possible transmission chains, phylodynamic inference combines evolutionary and epidemiological analyses to

estimate the parameters of the underlying epidemiological processes, allowing us to describe the overall dynamics of disease spread in the population. In this study, we introduce an approach to Mycobacterium tuberculosis (M. tuberculosis) phylodynamic analysis employing an existing computationally efficient model to quantify the transmission fitness costs of drug resistance with respect to drug-sensitive strains. To determine the accuracy and precision of our approach, we first perform a simulation study, mimicking the simultaneous spread of drug-sensitive and drug-resistant tuberculosis (TB) strains. We analyse the simulated transmission trees using the phylodynamic multi-type birth-death model (MTBD, (Kühnert et al., 2016)) within the BEAST2 framework and show that this model can estimate the parameters of the epidemic well, despite the simplifying assumptions that MTBD makes compared to the complex TB transmission dynamics used for simulation. We then apply the MTBD model to an M. tuberculosis lineage 4 dataset that primarily consists of MDR sequences. Some of the MDR strains additionally exhibit resistance to pyrazinamide - an important first-line anti-tuberculosis drug. Our results support the previously proposed hypothesis that pyrazinamide resistance confers a transmission fitness cost to the bacterium, which we quantify for the given dataset. Importantly, our sensitivity analyses show that the estimates are robust to different prior distributions on the resistance acquisition rate, but are affected by the size of the dataset - i.e. we estimate a higher fitness cost when using fewer sequences for analysis. Overall, we propose that MTBD can be used to quantify the transmission fitness cost for a wide range of pathogens where the strains can be appropriately divided into two or more categories with distinct properties.

DOI: 10.1016/j.epidem.2021.100471
PMID: 34256273

9. **Lesion Heterogeneity and Long-Term Heteroresistance in Multidrug-Resistant Tuberculosis.**

J Infect Dis. 2021 Sep 1;224(5):889-893. doi: 10.1093/infdis/jiab011.

Chen Y(1)(2), Ji L(2), Liu Q(1)(3), Li J(2), Hong C(2), Jiang Q(1)(2), Gan M(4), Takiff HE(5)(6)(7), Yu W(2), Tan W(2), Gao Q(1)(2).

Tuberculosis heteroresistance, in which only a fraction of the bacteria in a patient with tuberculosis contains drug-resistant mutations, has been a rising concern. However, its origins and prevalence remain elusive. Here, whole-genome sequencing was performed on 83 serial isolates from 31 patients with multidrug-resistant tuberculosis, and heteroresistance was detected in isolates

from 21 patients (67.74%). Heteroresistance persisted in the host for long periods, spanning months to years, and was associated with having multiple tubercular lesions. Our findings indicate that heteroresistance is common and persistent in patients with multidrug-resistant tuberculosis and may affect the success of their treatment regimens.

DOI: 10.1093/infdis/jiab011
PMID: 34467983

10. **Rifampicin mono-resistant tuberculosis is not the same as multidrug-resistant tuberculosis: a descriptive study from Khayelitsha, South Africa.**

Antimicrob Agents Chemother. 2021 Aug 30:AAC0036421. doi: 10.1128/AAC.00364-21. Online ahead of print.

Salaam-Dreyer Z(1), Streicher EM(2), Sirgel FA(2), Menardo F(3)(4), Borrell S(3)(4), Reinhard M(3)(4), Doetsch A(3)(4), Cudahy PGT(5), Mohr-Holland E(6), Daniels J(6), Dippenaar A(7), Nicol MP(8), Gagneux S(3)(4), Warren RM(2), Cox H(1)(9).

Rifampicin mono-resistant TB (RMR-TB, rifampicin resistance and isoniazid susceptibility) constitutes 38% of all rifampicin-resistant TB (RR-TB) in South Africa and is increasing. We aimed to compare RMR-TB with multidrug-resistant TB (MDR-TB) within a high TB, RR-TB and HIV burden setting. Patient-level clinical data and stored RR-TB isolates from 2008-2017 with available whole genome sequencing (WGS) data were used to describe risk factors associated with RMR-TB and to compare rifampicin-resistance (RR) conferring mutations between RMR-TB and MDR-TB. A subset of isolates with particular RR-conferring mutations were subjected to semi-quantitative rifampicin phenotypic drug susceptibility testing. Among 2,041 routinely diagnosed RR-TB patients, 463 (22.7%) had RMR-TB. HIV-positive individuals (adjusted Odds Ratio 1.4, 95% CI 1.1-1.9) and diagnosis between 2013-2017 versus 2008-2012 (aOR 1.3, 1.1-1.7) were associated with RMR-TB. Among 1,119 (54.8%) patients with available WGS data showing RR-TB, significant differences in the distribution of rpoB RR-conferring mutations between RMR-TB and MDR-TB isolates were observed. Mutations associated with high-level RR were more commonly found among MDR-TB isolates (811/889, 90.2% versus 162/230, 70.4% among RMR-TB, $p<0.0001$). In particular, the rpoB L430P mutation, conferring low-level RR, was identified in 32/230 (13.9%) RMR-TB versus 10/889 (1.1%) in MDR-TB ($p<0.0001$). Among 10 isolates with an rpoB L430P

mutation, 7 were phenotypically susceptible using the critical concentration of 0.5 µg/ml (range 0.125-1 µg/ml). The majority (215/230, 93.5%) of RMR-TB isolates showed susceptibility to all other TB drugs, highlighting the potential benefits of WGS for simplified treatment. These data suggest that the evolution of RMR-TB differs from MDR-TB with a potential contribution from HIV infection.

DOI: 10.1128/AAC.00364-21
PMID: 34460307

11. **Efficacy of bedaquiline in the treatment of drug-resistant tuberculosis: a systematic review and meta-analysis.**

BMC Infect Dis. 2021 Sep 17;21(1):970. doi: 10.1186/s12879-021-06666-8.

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

BACKGROUND: Drug-resistant tuberculosis (DR-TB) remains a major public health concern worldwide. Bedaquiline, a novel diarylquinoline, was added to the WHO-recommended all-oral regimen for patients with multidrug-resistant tuberculosis. We performed a systematic review and meta-analysis to determine the effect of bedaquiline on tuberculosis treatment outcomes.
METHODS: We searched the PubMed, Web of Science and EMBASE databases for relevant studies published up to March 12, 2021. We included studies in which some participants received bedaquiline and others did not. Stata version 16.0 (Stata Corp., College Station, Texas, USA) was used to analyze the results of the meta-analysis. Risk ratios (RRs) with 95% confidence intervals (95% CIs) were calculated to evaluate the effect of bedaquiline on drug-resistant tuberculosis. Between-study heterogeneity was examined by the I-squared test. Randomized controlled trials were assessed for quality using the Jadad scale, and cohort studies were assessed using the Newcastle-Ottawa scale.
RESULTS: Eight studies, including 2 randomized controlled trials and 6 cohort studies involving a total of 21,836 subjects, were included. When compared with the control, bedaquiline treatment was associated with higher rates of culture conversion (risk ratio (RR):1.272 (1.165-1.389), P < 0.001). We found substantial evidence of a significant reduction in all-cause death (RR: 0.529 (0.454-0.616), P < 0.001)) in the bedaquiline treatment group. There was no significant reduction in treatment success (RR = 0.980 (0.948-1.013, P = 0.234)).
CONCLUSIONS: This study demonstrated that compared with patients who do not receive bedaquiline, this drug has the potential to achieve a higher culture conversion rate and a lower mortality risk among drug-resistant tuberculosis cases.

DOI: 10.1186/s12879-021-06666-8
PMID: 34535090

12. **Molecular Epidemiology of Drug-Resistant Mycobacterium Tuberculosis in Japan.**

mSphere. 2021 Aug 25;6(4):e0097820. doi: 10.1128/mSphere.00978-20. Epub 2021 Jul 7.

Mizukoshi F(1), Kobayashi N(2)(3), Kirikae F(4), Ohta K(2)(5), Tsuyuguchi K(6), Yamada N(7), Inoue Y(6), Horiba M(8), Kawata N(9), Ichinose A(10)(11), Miyoshi-Akiyama T(11), Kiritani R(1), Funatogawa K(1), Kirikae T(4).

Clinical isolates of drug-resistant (isoniazid and/or rifampicin-resistant) Mycobacterium tuberculosis were obtained from 254 patients diagnosed with drug-resistant tuberculosis in Japan from April 2015 to March 2017 in National Hospital Organization hospitals. The 254 patients were approximately 32% of all 795 patients who were diagnosed with culture-confirmed drug-resistant tuberculosis from 2015 to 2016 nationwide in Japan. The whole-genome sequences of all the isolates from the 254 patients and the lineages of these isolates were determined, and phylogenetic trees were constructed based on single nucleotide polymorphism concatemers. Of these patients, 202 (79.5%) were born in Japan and 52 (20.5%) were born elsewhere. Of the 254 drug-resistant isolates, 54 (21.3%) were multidrug resistant, being resistant to both isoniazid and rifampicin. The percentages of multidrug-resistant isolates were significantly higher in foreign-born (38.5% [20/52]) than Japanese-born patients (16.8% [34/202]). Of the 54 multidrug-resistant isolates, nine were extensively drug resistant, which were all obtained from Japanese-born patients. Five extensively drug-resistant isolates were obtained from patients with incipient tuberculosis. A significant number of multidrug-resistant M. tuberculosis strains were isolated from foreign-born patients from Asian countries that have a high tuberculosis burden. Foreign-derived isolates affect the nationwide genetic diversity of drug-resistant M. tuberculosis in Japan. Extensively drug-resistant M. tuberculosis isolates were transmitted among the Japanese population. IMPORTANCE The incidence rate of tuberculosis (TB) in Japan was 11.5 per 100,000 of the population in 2019. Of TB patients in Japan, 61.1% were aged >70 years, and 10.7% were born outside Japan, mostly in Asian countries with a high burden of tuberculosis. Of the tuberculosis patients in the present study, 5.4% and 1.0% showed resistance to isoniazid and rifampicin, respectively, and 0.7% were multidrug resistant. The objective of this study was to clarify the molecular epidemiological properties of drug-resistant tuberculosis in Japan. Molecular epidemiology provides several clues to inform potential measures to control

drug-resistant tuberculosis in Japan.

DOI: 10.1128/mSphere.00978-20
PMCID: PMC8386464
PMID: 34232083

13. **Prevalence of Mycobacterium tuberculosis resistant to bedaquiline and delamanid in China.**

J Glob Antimicrob Resist. 2021 Sep;26:241-248. doi: 10.1016/j.jgar.2021.06.007. Epub 2021 Jun 30.

He W(1), Liu C(2), Liu D(3), Ma A(3), Song Y(4), He P(1), Bao J(5), Li Y(4), Zhao B(2), Fan J(2), Cheng Q(2), Zhao Y(6).

OBJECTIVES: The new antituberculous drugs delamanid and bedaquiline form the last line of defence against drug-resistant tuberculosis (TB). Understanding the background prevalence of resistance to new drugs can help predict the lifetime of these drugs' effectiveness and inform regimen design.
METHODS: Mycobacterium tuberculosis without prior exposure to novel anti-TB drugs were analysed retrospectively. Drug susceptibility testing for bedaquiline, delamanid, linezolid, clofazimine and widely used first- and second-line anti-TB drugs was performed. All TB isolates with resistance to new or repurposed drugs were subjected to whole-genome sequencing to explore the molecular characteristics of resistance and to perform phylogenetic analysis.
RESULTS: Overall, resistance to delamanid, bedaquiline, linezolid and clofazimine was observed in 0.7% (11/1603), 0.4% (6/1603), 0.4% (7/1603) and 0.4% (6/1603) of TB isolates, respectively. Moreover, 1.0% (1/102), 2.9% (3/102), 3.9% (4/102) and 1.0% (1/102) of multidrug-resistant TB (MDR-TB) were resistant to bedaquiline, delamanid, linezolid and clofazimine, respectively. Whereas 22.2% (2/9) of extensively-drug resistant tuberculosis (XDR-TB) isolates were resistant to both delamanid and linezolid, and none was resistant to bedaquiline or clofazimine. Phylogenetic analysis showed that recent transmission occurred in two XDR-TB with additional resistance to delamanid and linezolid. None known gene mutation associated with delamanid resistance was detected. All four isolates with cross-resistance to bedaquiline and clofazimine had a detected gene mutation in Rv0678. Three of five strains with linezolid resistance had a detected gene mutation in rplC.
CONCLUSION: Detection of resistance to new anti-TB drugs emphasises the pressing need for intensive surveillance for such resistance before their wide usage.

DOI: 10.1016/j.jgar.2021.06.007
PMID: 34214699

14. **Genomic-based surveillance reveals high ongoing transmission of multi-drug-resistant Mycobacterium tuberculosis in Southern Brazil.**

Int J Antimicrob Agents. 2021 Oct;58(4):106401. doi: 10.1016/j.ijantimicag.2021.106401. Epub 2021 Jul 18.

Salvato RS(1), Reis AJ(2), Schiefelbein SH(3), Gómez MAA(2), Salvato SS(4), da Silva LV(4), Costa ERD(5), Unis G(6), Dias CF(6), Viveiros M(7), Portugal I(8), von Groll A(2), da Silva PEA(2), Kritski AL(5), Perdigão J(8), Rossetti MLR(9).

Genomic-based surveillance on the occurrence of drug resistance and its transmission dynamics has emerged as a powerful tool for the control of tuberculosis (TB). A whole-genome sequencing approach, phenotypic testing and clinical-epidemiological investigation were used to undertake a retrospective population-based study on drug-resistant (DR)-TB in Rio Grande do Sul, the largest state in Southern Brazil. The analysis included 305 resistant Mycobacterium tuberculosis strains sampled statewide from 2011 to 2014, and covered 75.7% of all DR-TB cases identified in this period. Lineage 4 was found to be predominant (99.3%), with high sublineage-level diversity composed mainly of 4.3.4.2 [Latin American and Mediterranean (LAM)/RD174], 4.3.3 (LAM/RD115) and 4.1.2.1 (Haarlem/RD182) sublineages. Genomic diversity was also reflected in resistance of the variants to first-line drugs. A large number of distinct resistance-conferring mutations, including variants that have not been reported previously in any other setting worldwide, and 22 isoniazid-monoresistant strains with mutations described as disputed in the rpoB gene but causing rifampicin resistance generally missed by automated phenotypic tests as BACTEC MGIT. Using a cut-off of five single nucleotide polymorphisms, the estimated recent transmission rate was 55.1%, with 168 strains grouped into 28 genomic clusters. The most worrying fact concerns multi-drug-resistant (MDR) strains, of which 73.4% were clustered. Different resistance profiles and acquisition of novel mutations intraclusters revealed important amplification of resistance in the region. This study described the diversity of M. tuberculosis strains, the basis of drug resistance, and ongoing transmission dynamics across the largest state in Southern Brazil, stressing the urgent need for MDR-TB transmission control state-wide.

DOI: 10.1016/j.ijantimicag.2021.106401
PMID: 34289403

15. **Drug resistant tuberculosis cases from the Copperbelt province and Northern regions of Zambia: Genetic diversity, demographic and clinical characteristics.**

Tuberculosis (Edinb). 2021 Sep 2;130:102122. doi: 10.1016/j.tube.2021.102122. Online ahead of print.

Chisompola NK(1), Streicher EM(2), Dippenaar A(2), Whitfield MG(2), Tembo M(3), Mwanza S(3), Warren RM(2), Sampson SL(4).

Tuberculosis (TB) caused by Mycobacterium tuberculosis remains a major cause of death worldwide. Diverse genotypes have been demonstrated to drive the epidemiology of drug resistant (DR-) TB globally. Currently, there is limited knowledge on the genotypes and transmission dynamics of M. tuberculosis in Zambia. This study aimed to describe the genotypes of DR-TB from the Copperbelt and Northern regions of Zambia. Molecular typing tools of insertion sequence 6110-restriction fragment length polymorphism (IS6110-RFLP) and spacer oligonucleotide typing (spoligotyping) were applied. We demonstrate that diverse genotypes are associated with DR-TB in Zambia. The predominant genotype was lineage 4; other strains belonged to lineage 2 and 3. Genotypes previously identified as driving the epidemiology of drug susceptible TB have been identified as drivers of DR-TB. Genotyping analysis showed clustering of strains among patients from different regions of the country; suggesting that DR-TB is widespread. Molecular findings combined with phenotypic and epidemiologic findings play a critical role in identifying circulating genotypes and possible transmission chains. Clustering of drug resistant strains was demonstrated to be 48% and 86% according to IS6110-RFLP and spoligotyping, respectively. However, gaps in clinical and demographic data skew the interpretation, and call for data collection policy improvements.

DOI: 10.1016/j.tube.2021.102122
PMID: 34517268

16. **TB or not TB? Definitive determination of species within the Mycobacterium tuberculosis complex in unprocessed sputum from adults with presumed multidrug-resistant tuberculosis.**

Trop Med Int Health. 2021 Sep;26(9):1057-1067. doi: 10.1111/tmi.13638. Epub 2021 Jun 24.

Mbelele PM(1)(2), Sauli E(2), Mpolya EA(2), Mohamed SY(3), Addo KK(4), Mfinanga SG(5)(6), Heysell SK(3), Mpagama S(1)(2).

OBJECTIVES: Differences among Mycobacterium tuberculosis complex (MTC) species may predict drug resistance or treatment success. Thus, we optimised and deployed the genotype MTBC assay (gMTBC) to identify MTC to the species level, and then performed comparative genotypic drug-susceptibility testing to anti-tuberculosis drugs from direct sputum of patients with presumed multidrug-resistant tuberculosis (MDR-TB) by the MTBDRplus/sl reference method.
METHODS: Patients with positive Xpert® MTB/RIF (Xpert) results were consented to provide early-morning-sputum for testing by the gMTBC and the reference MTBDRplus/sl. Chi-square or Fisher's exact test compared proportions. Modified Poisson regression modelled detection of MTC by gMTBC.
RESULTS: Among 73 patients, 53 (73%) were male and had a mean age of 43 (95% CI; 40-45) years. In total, 34 (47%), 36 (49%) and 38 (55%) had positive gMTBC, culture and MTBDR respectively. Forty patients (55%) had low quantity MTC by Xpert, including 31 (78%) with a negative culture. gMTBC was more likely to be positive in patients with chest cavity 4.18 (1.31-13.32, P = 0.016), high-quantity MTC by Xpert 3.03 (1.35-6.82, P = 0.007) and sputum smear positivity 1.93 (1.19-3.14, P = 0.008). The accuracy of gMTBC in detecting MTC was 95% (95% CI; 86-98; κ = 0.89) compared to MTBDRplus/sl. All M. tuberculosis/canettii identified by gMTB were susceptible to fluoroquinolone and aminoglycosides/capreomycin.
CONCLUSIONS: The concordance between the gMTBC assay and MTBDRplus/sl in detecting MTC was high but lagged behind the yield of Xpert MTB/RIF. All M. tuberculosis/canettii were susceptible to fluoroquinolones, a core drug in MDR-TB treatment regimens.

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PMID: 34107112

17. **Survival Status and Predictors of Mortality among Multidrug-Resistant Tuberculosis Patients in Saint Peter's Specialized Hospital, Addis Ababa, Ethiopia.**

Can J Infect Dis Med Microbiol. 2021 Sep 3;2021:6696199. doi: 10.1155/2021/6696199. eCollection 2021.

Muluneh MA(1), Zeru AB(2), Derseh BT(2), Molla Kebede A(3).

BACKGROUND: Multidrug-Resistant Tuberculosis (MDR-TB) is tuberculosis that is resistant to at least both rifampicin and isoniazid. The World Health Organization as reported in 2019 revealed that Ethiopia is among the 20 countries with the highest estimated numbers of incident MDR-TB cases. However, supporting evidence is limited in the study area after the Ethiopian national strategic plan for tuberculosis prevention and control is started.
OBJECTIVE: To determine survival status and predictors of mortality among multidrug-resistant tuberculosis patients treated in Saint Peter's Specialized Hospital at Addis Ababa, Ethiopia, 2020.
METHODS: An institutional retrospective cohort study was conducted using all MDR-TB patients who were enrolled in Saint. Peter's Specialized Hospital from January 01, 2015, to December 31, 2017. A pretested data extraction form that had 5 items for sociodemographic and 15 items for the measurement of clinical characteristics of 484 MDR-TB patients was used. STATA software version 14.2 was used for data cleaning and analysis. A variable that fitted in the bivariable Cox proportional hazard model at p value <0.25 was used in the final multivariable Cox proportional hazard model, and independent predictors of time to event were determined at a p value of 0.05.
RESULT: A total of 484 patients were followed up for 5,078 person-months. Among the total patients, nearly half, 238 (48.8%), were males. The median age of patients was 30 years (interquartile range (IQR), 24-39), and 56 (11.6%) were aged between 1 and 19 years. During the follow-up period, 315 (65.1%) patients were cured, 125 (25.8%) completed treatment, 24 (5%) died, and 20 (4.1%) were lost to follow-up. The overall cumulative probability survival of the patients at the end of treatment was 94.85% (95% confidence interval (CI): 92.38%-96.53%). The independent predictors of time to death were being anemic (AHR = 3.65; 95% CI: 1.36, 9.79), having clinical complication (AHR = 3; 95% CI: 1.2, 7.5), and being HIV infected (AHR = 5.8; 95% CI: 2.2, 15.7).
CONCLUSIONS: MDR-TB patients' survival rate was high in St Peter's Specialized Hospital. MDR-TB patients with anemia, HIV coinfection, and clinical complications had higher risk of mortality. So, prevention and controlling of anemia, HIV/AIDS, and clinical complications will reduce the mortality of MDR-TB patients.

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PMCID: PMC8437643
PMID: 34527088

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

J Ethnopharmacol. 2021 Sep 15;282:114641. doi: 10.1016/j.jep.2021.114641. Online ahead of print.

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

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

folklore use of U. laevis for treating Tb, and the key biomarker metabolites were found to be 1 and 4. Hence, it can be concluded that U. laevis can be used as a potential source for the novel drug development for MDR-Tb.

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

19. **Prediction of Multidrug-Resistant Tuberculosis Using Machine Learning Algorithms in SWAT, Pakistan.**

J Healthc Eng. 2021 Aug 31;2021:2567080. doi: 10.1155/2021/2567080. eCollection 2021.

Ali MH(1)(2), Khan DM(1), Jamal K(2), Ahmad Z(3), Manzoor S(4), Khan Z(1).

In this paper, we have focused on machine learning (ML) feature selection (FS) algorithms for identifying and diagnosing multidrug-resistant (MDR) tuberculosis (TB). MDR-TB is a universal public health problem, and its early detection has been one of the burning issues. The present study has been conducted in the Malakand Division of Khyber Pakhtunkhwa, Pakistan, to further add to the knowledge on the disease and to deal with the issues of identification and early detection of MDR-TB by ML algorithms. These models also identify the most important factors causing MDR-TB infection whose study gives additional insights into the matter. ML algorithms such as random forest, k-nearest neighbors, support vector machine, logistic regression, leaset absolute shrinkage and selection operator (LASSO), artificial neural networks (ANNs), and decision trees are applied to analyse the case-control dataset. This study reveals that close contacts of MDR-TB patients, smoking, depression, previous TB history, improper treatment, and interruption in first-line TB treatment have a great impact on the status of MDR. Accordingly, weight loss, chest pain, hemoptysis, and fatigue are important symptoms. Based on accuracy, sensitivity, and specificity, SVM and RF are the suggested models to be used for patients' classifications.

DOI: 10.1155/2021/2567080
PMCID: PMC8426057
PMID: 34512933

20. **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.

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

21. **Prevalence of drug resistance-conferring mutations associated with isoniazid- and rifampicin-resistant Mycobacterium tuberculosis in Ethiopia: a systematic review and meta-analysis.**

J Glob Antimicrob Resist. 2021 Sep;26:207-218. doi: 10.1016/j.jgar.2021.06.009.

Epub 2021 Jun 30.

Reta MA(1), Alemnew B(2), Abate BB(3), Fourie PB(4).

OBJECTIVES: Globally, the incidence and mortality of tuberculosis (TB) are declining; however, low detection of drug-resistant disease threatens to reverse current progress toward global TB control. Multiple rapid molecular diagnostic tests have recently been developed to detect genetic mutations in Mycobacterium tuberculosis (Mtb) known to confer drug resistance. However, their utility depends on the frequency and distribution of resistance-associated mutations in the pathogen population. This review aimed to assess the prevalence of gene mutations associated with rifampicin (RIF)- and isoniazid (INH)-resistant Mtb in Ethiopia.
METHODS: We searched the literature in PubMed/MEDLINE, Web of Science, Scopus and Cochrane Library. Data analysis was conducted in Stata 11.
RESULTS: Totally, 909 (95.8%) of 949 INH-resistant Mtb isolates had detectable gene mutations: 95.8% in katG315 and 5.9% in the inhA promoter region. Meta-analysis resulted in an estimated pooled prevalence of katGMUT1(S315T1) of 89.2% (95% CI 81.94-96.43%) and a pooled prevalence of inhAMUT1(C15T) of 77.5% (95% CI 57.84-97.13%). Moreover, 769 (90.8%) of 847 RIF-resistant strains had detectable rpoB gene mutations. Meta-analysis resulted in a pooled prevalence of rpoBMUT3(S531L) of 74.2% (95% CI 66.39-82.00%).
CONCLUSION: RIF-resistant Mtb were widespread, particularly those harbouring rpoB(S531L) mutation. Similarly, INH-resistant Mtb with katG(S315T1) and inhA(C15T) mutations were common. Tracking S531L, S315T1 and C15T mutations among RIF- and INH-resistant isolates, respectively, would be diagnostically and epidemiologically valuable. Rapid diagnosis of RIF- and INH-resistant Mtb would expedite modification of TB treatment regimens, and proper timely infection control interventions could reduce the risk of development and transmission of multidrug-resistant TB.

DOI: 10.1016/j.jgar.2021.06.009
PMID: 34214698

22. **Genetic diversity and primary drug resistance transmission in Mycobacterium tuberculosis in southern Mexico.**

Infect Genet Evol. 2021 Sep;93:104994. doi: 10.1016/j.meegid.2021.104994. Epub 2021 Jul 7.

Ordaz-Vázquez A(1), Torres-González P(1), Cruz-Hervert P(2), Ferreyra-Reyes

L(3), Delgado-Sánchez G(3), García-García L(3), Kato-Maeda M(4), Ponce-De-León A(1), Sifuentes-Osornio J(5), Bobadilla-Del-Valle M(6).

Tuberculosis is a global human health threat, especially in developing countries. The present study aimed to describe the genetic diversity of Mycobacterium tuberculosis and to measure the transmission rates of primary and acquired resistance. A total of 755 M. tuberculosis isolates from a cohort study of patients with culture-confirmed pulmonary tuberculosis in Orizaba, Veracruz, performed between 1995 and 2010 were genotyped by the 24-locus mycobacterial interspersed repetitive unit-variable number of tandem repeats (MIRU-VNTR) method. Drug susceptibility was determined. Logistic regression models were constructed to identify the variables associated with resistance and clusters. The recent transmission index (RTI), the Hunter-Gaston discrimination index (HGDI) for the MIRU-VNTR test and allelic diversity (h) were calculated. The Haarlem and LAM lineages were the most common in the population. A total of 519 isolates were grouped into 128 clusters. The overall drug resistance rate was 19%, isoniazid monoresistance (10%) was the most common, and 3.4% of the isolates were multidrug resistant. Among the 116 isolates resistant to at least one drug, the primary and acquired resistance rates were 81.9% and 18.1%, respectively. Primary resistance was associated with belonging to a cluster (aOR 4.05, 95% CI 1.5-11.2, p = 0.007). Previous treatment history (aOR 9.05, 95% CI 3.6-22.5, p < 0.001) and LAM lineage (aOR 4.25, 95% CI 1.4-12.7, p = 0.010) were associated with multidrug-resistant tuberculosis (MDR-TB). The RTI was 51.7%, and the 24-locus MIRU-VNTR HGDI was 0.98. The alleles with the greatest diversity were 4056-QUB26 (h = 0.84), 2163b-QUB11b (h = 0.79), and 424-Mtub04 (h = 0.72). Primary resistance transmission, high LAM lineage prevalence and its association with MDR-TB represent public health problems. The implementation of molecular tools is needed to improve the existing control surveillance tuberculosis program.

DOI: 10.1016/j.meegid.2021.104994
PMID: 34245908

23. **Effect of Isoniazid Intake on Ethionamide Pharmacokinetics and Target Attainment in Multidrug-Resistant Tuberculosis Patients.**

Antimicrob Agents Chemother. 2021 Sep 17;65(10):e0027821. doi: 10.1128/AAC.00278-21. Epub 2021 Jul 26.

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. This study was conducted to (i) describe the distribution of ethionamide MICs, (ii) describe the pharmacokinetics of ethionamide, and (iii) determine the probability of attaining target area under the concentration-time curve from 0 to 24 h (AUC0-24)/MIC values associated with suppression of resistant subpopulation and microbial kill. Participants received 15 to 20 mg of drug/kg of body weight of ethionamide daily (in 500- or 750-mg doses) as part of a multidrug regimen. Pretreatment MICs of ethionamide for Mycobacterium tuberculosis sputum isolates were determined using Sensititre MYCOTB MIC plates. Plasma concentrations of ethionamide (measured predose and at 2, 4, 6, 8, and 10 h postdose) 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 coadministration reduced ethionamide clearance by 31%, resulting in a 44% increase in AUC0-24. The median (range) MIC (n = 111) was 2.5 mg/liter (<0.3 to >40 mg/liter). Simulations showed increased daily doses of ethionamide (1,250 mg, 1,500 mg, and 1,750 mg for patients weighing ≤45 kg, 46 to 70 kg, and >70 kg, respectively) resulted in the probability of attaining an area under the concentration-time curve from 0 to 24 h for the free, unbound fraction of a drug (fAUC0-24)/MIC ratio of ≥42 in more than 90% of patients only at the lowest MIC of 0.3 mg/liter. 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

24. **Insignificant difference in culture conversion between bedaquiline-containing and bedaquiline-free all-oral short regimens for multidrug-resistant tuberculosis.**

Int J Infect Dis. 2021 Aug 25;111:138-147. doi: 10.1016/j.ijid.2021.08.055. Online ahead of print.

Fu L(1), Weng T(2), Sun F(2), Zhang P(1), Li H(1), Li Y(2), Yang Q(3), Cai Y(4), Zhang X(5), Liang H(6), Chen X(4), Wang Z(1), Liu L(7), Zhang W(8), Deng G(9).

BACKGROUND: Multidrug-resistant tuberculosis (MDR-TB) patients have been suffering long, ineffective, and toxic treatment until short-course injectable-free regimens emerged. However, the new WHO-recommended regimens might be less feasible in the real-world setting. Here, we evaluated two optimized all-oral short-course regimens in China.

METHODS: From April 2019 to August 2020, we conducted a prospective nonrandomized controlled trial and consecutively included 103 MDR-TB patients diagnosed with pulmonary MDR-TB in Shenzhen, China. A 4-5 drug regimen of 9-12 months was tailored to the strain's resistance patterns, patients' affordability, and tolerance to drugs. This was an interim analysis, focusing on the early treatment period.
RESULTS: 53.4% (55/103) of patients were prescribed linezolid, fluoroquinolone (FQ), clofazimine, cycloserine, and pyrazinamide, followed by a regimen in which clofazimine was replaced by bedaquiline (35/103, 34.0%). The culture conversion rate was 83.1% and 94.4% at two and four months, respectively, with no significant difference between bedaquiline-free and bedaquiline-containing cases and between FQ-susceptible and FQ-resistant cases. Among 41 patients who completed treatment, 40 (97.6%) patients had a favorable outcome and no relapse was observed. Peripheral neuropathy and arthralgia/myalgia were the most frequent AEs (56.3%, 58/103). 18 AEs caused permanent discontinuation of drugs, mostly due to pyrazinamide and linezolid.
CONCLUSION: Optimized all-oral short-course regimens showed satisfactory efficacy and safety in early treatment stage. Further research is needed to confirm these results.

DOI: 10.1016/j.ijid.2021.08.055
PMID: 34454119

25. **Prevalence and Molecular Characteristics Based on Whole Genome Sequencing of Mycobacterium tuberculosis Resistant to Four Anti-Tuberculosis Drugs from Southern Xinjiang, China.**

Infect Drug Resist. 2021 Aug 24;14:3379-3391. doi: 10.2147/IDR.S320024. eCollection 2021.

Anwaierjiang A(#)(1), Wang Q(#)(2), Liu H(#)(3), Yin C(1), Xu M(2), Li M(3), Liu M(1), Liu Y(2), Zhao X(3), Liu J(1), Li G(3), Mijiti X(2), Wan K(3).

OBJECTIVE: Drug-resistant tuberculosis is a major public health problem, especially in the southern region of Xinjiang, China; however, there is little information regarding drug resistance profiles and mechanism of Mycobacterium tuberculosis in this area. The aim of this study was to determine the prevalence and molecular characteristics of M. tuberculosis resistant to four anti-tuberculosis drugs from this area.
METHODS: Three hundred and forty-six isolates from the southern region of Xinjiang, China were included and used to perform phenotypic drug susceptibility

testing and whole genome sequencing (WGS). Mutations in seven loci associated with drug resistance, including rpoB for rifampicin (RMP), katG, inhA promoter and oxyR-ahpC for isoniazid (INH), rrs 530 and 912 loops and rpsL for streptomycin (STR), and embB for ethambutol (EMB), were characterized.
RESULTS: Among 346 isolates, 106, 60, 70 and 29 were resistant to INH, RMP, STR and EMB, respectively; 132 were resistant to at least one of the four anti-tuberculosis drugs and 51 were multi-drug resistant (MDR). Beijing genotype and retreated patients showed a significantly increased risk for developing MDR tuberculosis. Compared with the phenotypic data, the sensitivity and specificity for WGS to predict resistance were 96.7% and 98.6% for RMP, 75.5% and 97.1% for INH, 68.6% and 99.6% for STR, 93.1% and 93.7% for EMB, respectively. The most common mutations conferring RMP, INH, STR and EMB resistance were Ser450Leu (51.7%) in rpoB, Ser315Thr (44.3%) in katG, Lys43Arg (35.7%) in rpsL and Met306Val (24.1%) in embB.
CONCLUSION: This study provides the first information on the prevalence and molecular characters of drug resistant M. tuberculosis in the southern region of Xinjiang, China, which will be helpful for choosing early detection methods for drug resistance (ig, molecular methods) and subsequently initiation of proper therapy of tuberculosis in this area.

DOI: 10.2147/IDR.S320024
PMCID: PMC8402983
PMID: 34466004

26. **The burden of drug resistant tuberculosis in a predominantly nomadic population in Uganda: a mixed methods study.**

BMC Infect Dis. 2021 Sep 14;21(1):950. doi: 10.1186/s12879-021-06675-7.

Simbwa BN(1), Katamba A(2), Katana EB(3), Laker EAO(4), Nabatanzi S(3), Sendaula E(3), Opio D(3), Ictho J(5), Lochoro P(5), Karamagi CA(3)(6), Kalyango JN(3), Worodria W(2)(7).

BACKGROUND: Emergence of drug resistant tuberculosis (DR-TB) has aggravated the tuberculosis (TB) public health burden worldwide and especially in low income settings. We present findings from a predominantly nomadic population in Karamoja, Uganda with a high-TB burden (3500 new cases annually) and sought to determine the prevalence, patterns, factors associated with DR-TB.
METHODS: We used mixed methods of data collection. We enrolled 6890 participants who were treated for tuberculosis in a programmatic setting between January 2015 and April 2018. A cross sectional study and a matched case control study with

conditional logistic regression and robust standard errors respectively were used to the determine prevalence and factors associated with DR-TB. The qualitative methods included focus group discussions, in-depth interviews and key informant interviews.
RESULTS: The overall prevalence of DR-TB was 41/6890 (0.6%) with 4/64,197 (0.1%) among the new and 37/2693 (1.4%) among the previously treated TB patients respectively. The drug resistance patterns observed in the region were mainly rifampicin mono resistant (68.3%) and Multi Drug-Resistant Tuberculosis (31.7%). Factors independently associated with DR-TB were previous TB treatment, adjusted odds ratio (aOR) 13.070 (95%CI 1.552-110.135) and drug stock-outs aOR 0.027 (95%CI 0.002-0.364). The nomadic lifestyle, substance use, congested homesteads and poor health worker attitudes were a great challenge to effective treatment of TB.
CONCLUSION: Despite having the highest national TB incidence, Karamoja still has a low DR-TB prevalence. Previous TB treatment and drug stock outs were associated with DR-TB. Regular supply of anti TB medications and health education may help to stem the burden of TB disease in this nomadic population.

DOI: 10.1186/s12879-021-06675-7
PMCID: PMC8442422
PMID: 34521382

27. **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.

DOI: 10.1007/s00203-021-02387-3
PMID: 34032874 [Indexed for MEDLINE]

28. **Emergence of bedaquiline-resistance in a high-burden country of tuberculosis.**

Eur Respir J. 2021 Sep 9:2100621. doi: 10.1183/13993003.00621-2021. Online ahead of print.

Chesov E(1)(2)(3)(4)(5), Chesov D(1)(3)(4)(5), Maurer FP(6)(7), Andres S(6), Utpatel C(8), Barilar I(8), Donica A(2), Reimann M(3)(4)(9), Niemann S(3)(6)(8), Lange C(3)(4)(9)(10)(11), Crudu V(2), Heyckendorf J(3)(4)(9)(5), Merker M(12)(8)(13)(5).

RATIONALE: Bedaquiline has been classified as a Group A drug for the treatment of multidrug-resistant tuberculosis (MDR-TB) by the World Health Organization, however globally emerging resistance threatens the effectivity of novel MDR-TB treatment regimens.
OBJECTIVES: We analysed pre-existing and emerging bedaquiline resistance in bedaquiline-based MDR-TB therapies, and risk factors associated with treatment failure and death.
METHODS: In a cross-sectional cohort study, we employed patient data, whole genome sequencing (WGS) and phenotyping of Mycobacterium tuberculosis complex (MTBC) isolates. We could retrieve baseline isolates from 30.5% (62/203) of all MDR-TB patients who received bedaquiline between 2016 and 2018 in the Republic of Moldova. This includes 26 patients for whom we could also retrieve a follow-up isolate.
MEASUREMENTS AND MAIN RESULTS: At baseline, all MTBC isolates were susceptible

to bedaquiline. Among 26 patients with available baseline and follow-up isolates, 4/26 (15.3%) patients harbored strains which acquired bedaquiline resistance under therapy, while 1/26 (3.8%) patients was re-infected with a second bedaquiline resistant strain. Treatment failure and death were associated with cavitary disease (p=0.011), and any additional drug prescribed in the bedaquiline containing regimen with WGS-predicted resistance at baseline (p=0.012, OR 1.92 per unit increase, 95%CI 1.15-3.21).
CONCLUSIONS: MDR-TB treatments based on bedaquiline require a functional background regimen to achieve high cure rates and to prevent the evolution of bedaquiline resistance. Novel MDR-TB therapies with bedaquiline require timely and comprehensive drug resistance monitoring.

DOI: 10.1183/13993003.00621-2021
PMID: 34503982

29. **Capturing patient-reported and quality of life outcomes with use of shorter regimens for drug-resistant tuberculosis: mixed-methods substudy protocol, TB PRACTECAL-PRO.**

BMJ Open. 2021 Sep 6;11(9):e043954. doi: 10.1136/bmjopen-2020-043954.

Stringer B(1), Lowton K(2), James N(3), Nyang'wa BT(3)(4).

INTRODUCTION: People living with multidrug-resistant tuberculosis currently have few options for effective treatment and cure. Regimens that are available are toxic, may involve injections and take up to 2 years to complete treatment, with success rates as low as 50%. The TB-PRACTECAL trial is evaluating shorter, more tolerable regimens of oral drugs; we detail the substudy within this trial, PRACTECAL-PRO, which aims to evaluate patient experiences and perspectives on treatment, to understand outcomes more fully.
METHODS AND ANALYSIS: We are conducting a mixed-methods evaluation within both investigational and standard of care arms within the TB-PRACTECAL trial, using sequential quality of life (QoL) surveys and in-depth interviews. Data collection involves the Short Form 12 (SF-12) and St George's Respiratory Questionnaire (SGRQ), collected at up to four fixed timepoints, from baseline, to up to 12 months later. Healthy volunteers will be surveyed to establish locally relevant controls. We will also purposively sample participants for qualitative data collection and analysis, to provide rich explanation of QoL scores. The study will be implemented in all six TB-PRACTECAL study sites in Uzbekistan, South Africa and Belarus. QoL surveys will be scored and analysed according to SF-12 and SGRQ developers' manuals. Differences between scores at

baseline and later timepoints will be evaluated as well as graphical exploration of group score trajectories of investigational and standard of care arms.
ETHICS AND DISSEMINATION: Ethics approval was obtained from the Médecins Sans Frontières Ethics Review Board. Local ethics approval has been obtained in Uzbekistan, Belarus and South Africa. Results of the substudy will be shared with local health authorities, the WHO and submitted for publication in a peer-reviewed journal.
TRIAL REGISTRATION NUMBER: NCT03942354; Pre-results.

DOI: 10.1136/bmjopen-2020-043954
PMID: 34489263 [Indexed for MEDLINE]

30. **Evaluation of Multidrug Resistant Loop-mediated Isothermal Amplification Assay for Detecting the Drug Resistance of Mycobacterium tuberculosis.**

Biomed Environ Sci. 2021 Aug 20;34(8):616-622. doi: 10.3967/bes2021.085.

Liu CF(1), Song YM(2), He P(3), Liu DX(4), He WC(3), Li YM(2), Zhao YL(1).

OBJECTIVE: To evaluate multidrug resistant loop-mediated isothermal amplification (MDR-LAMP) assay for the early diagnosis of multidrug-resistant tuberculosis and to compare the mutation patterns associated with the rpoB, katG, and inhA genes at the Chinese Center for Disease Control and Prevention.
METHODS: MDR-LAMP assay was evaluated using 100 Mycobacterium tuberculosis (Mtb) isolates obtained from the National Reference Laboratory for Tuberculosis in China. Phenotypic resistance to isoniazid and rifampicin and whole-genome sequencing served as reference standards.
RESULTS: The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of MDR-LAMP were 85.5%, 93.6%, 96.7%, and 74.4% for the detection of resistance to isoniazid and rifampicin, respectively, and 80.5%, 92.3%, 98.6%, and 41.4% for the detection of Mtb cultured from smear-positive sputum samples, respectively. When DNA sequencing was used as the reference standard, the sensitivity, specificity, PPV, and NPV of MDR-LAMP were 93.1%, 92.3%, 97.2%, and 82.8% for the detection of katG and inhA gene mutations, respectively, and 89.1%, 88.9%, 93.4%, and 81.1% for the detection of rpoB gene mutation, respectively.
CONCLUSION: MDR-LAMP is a rapid and accessible assay for the laboratory identification of rifampicin and isoniazid resistance of Mtb isolates.

DOI: 10.3967/bes2021.085
PMID: 34474721

31. **Prediction of anti-tuberculosis treatment duration based on a 22-gene transcriptomic model.**

Eur Respir J. 2021 Sep 2;58(3):2003492. doi: 10.1183/13993003.03492-2020. Print 2021 Sep.

Heyckendorf J(1)(2)(3)(4), Marwitz S(5)(6)(4), Reimann M(7)(2)(3)(4), Avsar K(8), DiNardo AR(9), Günther G(10)(11), Hoelscher M(12)(13), Ibraim E(14), Kalsdorf B(7)(2)(3), Kaufmann SHE(15)(16)(17), Kontsevaya I(7)(2)(3), van Leth F(18)(19), Mandalakas AM(9), Maurer FP(20)(21), Müller M(22), Nitschkowski D(5)(6), Olaru ID(23)(24), Popa C(14), Rachow A(12)(13), Rolling T(2)(25)(26), Rybniker J(27)(28)(29), Salzer HJF(30), Sanchez-Carballo P(7)(2)(3), Schuhmann M(31), Schaub D(7)(2)(3), Spinu V(14), Suárez I(27), Terhalle E(7)(2)(3), Unnewehr M(32)(33), Weiner J 3rd(34), Goldmann T(5)(6)(4), Lange C(7)(2)(3)(35)(4).

BACKGROUND: The World Health Organization recommends standardised treatment durations for patients with tuberculosis (TB). We identified and validated a host-RNA signature as a biomarker for individualised therapy durations for patients with drug-susceptible (DS)- and multidrug-resistant (MDR)-TB.
METHODS: Adult patients with pulmonary TB were prospectively enrolled into five independent cohorts in Germany and Romania. Clinical and microbiological data and whole blood for RNA transcriptomic analysis were collected at pre-defined time points throughout therapy. Treatment outcomes were ascertained by TBnet criteria (6-month culture status/1-year follow-up). A whole-blood RNA therapy-end model was developed in a multistep process involving a machine-learning algorithm to identify hypothetical individual end-of-treatment time points.
RESULTS: 50 patients with DS-TB and 30 patients with MDR-TB were recruited in the German identification cohorts (DS-GIC and MDR-GIC, respectively); 28 patients with DS-TB and 32 patients with MDR-TB in the German validation cohorts (DS-GVC and MDR-GVC, respectively); and 52 patients with MDR-TB in the Romanian validation cohort (MDR-RVC). A 22-gene RNA model (TB22) that defined cure-associated end-of-therapy time points was derived from the DS- and MDR-GIC data. The TB22 model was superior to other published signatures to accurately predict clinical outcomes for patients in the DS-GVC (area under the curve 0.94, 95% CI 0.9-0.98) and suggests that cure may be achieved with shorter treatment durations for TB patients in the MDR-GIC (mean reduction 218.0 days, 34.2%;

p<0.001), the MDR-GVC (mean reduction 211.0 days, 32.9%; p<0.001) and the MDR-RVC (mean reduction of 161.0 days, 23.4%; p=0.001).
CONCLUSION: Biomarker-guided management may substantially shorten the duration of therapy for many patients with MDR-TB.

DOI: 10.1183/13993003.03492-2020
PMID: 33574078

32. **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

33. **Active surveillance for adverse events in patients on longer treatment regimens for multidrug-resistant tuberculosis in Viet Nam.**

PLoS One. 2021 Sep 7;16(9):e0255357. doi: 10.1371/journal.pone.0255357. eCollection 2021.

Ngoc NB(1)(2)(3), Vu Dinh H(3), Thuy NT(1)(2), Quang DV(3), Huyen CTT(3), Hoa NM(3), Anh NH(3), Dat PT(1), Hoa NB(1), Tiemersma E(4), Nhung NV(1).

OBJECTIVE: Management of multidrug-resistant tuberculosis (MDR-TB) is a significant challenge to the global healthcare system due to the complexity and long duration of the MDR-TB treatment. This study analyzed the safety of patients on longer injectable-based MDR-TB treatment regimens using active pharmacovigilance data.
METHOD: We conducted an observational, prospective study based on active pharmacovigilance within the national TB program. A total of 659 MDR-TB patients were enrolled and followed up at 9 TB- hospitals in 9 provinces of all 3 regions in Vietnam between 2014 and 2016. Patients received a treatment regimen (standardized or individualized) based on their drug susceptibility test result and their treatment history. Baseline and follow-up information was collected at the start and during treatment. Adverse events (AE) were defined and classified as serious adverse events (SAEs) or otherwise. Multivariate Cox regression following the Iterative Bayesian Model Averaging algorithm was performed to identify factors associated with AE occurrence.
RESULTS: Out of 659 patients assessed, 71.3% experienced at least one AE, and 17.5% suffered at least one SAE. The most common AEs were gastrointestinal disorders (38.5%), arthralgia (34.7%), and psychiatric disorders (30.0%). The proportion of patients with nephrotoxicity and hearing loss or vestibular disorders were 7.4% and 15.2%, respectively. 13.1% of patients required modifications or interruption of one or more drugs. In 77.7% of patients, treatment was completed successfully, while 9.3% lost to follow-up, in 3.0% treatment failed, and 7.4% died. Some significant risk factors for nephrotoxicity included diabetes mellitus (HR = 8.46 [1.91-37.42]), renal dysfunction (HR = 8.46 [1.91-37.42]), alcoholism (HR = 13.28 [5.04-34.99]), and a higher average daily dose of injectable drugs (HR = 1.28 [1.14-1.43]).
CONCLUSION: While a majority of patients on the longer injectable-based regimens experienced non-serious AEs during MDR-TB treatment, one in six patients experienced at least an SAE. Active TB drug-safety monitoring is useful to

understand the safety of MDR-TB treatment and explore the risk factors for toxicity. All-oral, shorter MDR-TB regimens might be able to reduce the inconvenience, discomfort, and toxicity of such regimens and increase adherence and likelihood of successful completion.

DOI: 10.1371/journal.pone.0255357
PMCID: PMC8423256
PMID: 34492031

34. **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.

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

35. **Recent Advances in Diagnosis and Management of Female Genital Tuberculosis.**

J Obstet Gynaecol India. 2021 Aug 28:1-12. doi: 10.1007/s13224-021-01523-9. Online ahead of print.

Sharma JB(1), Sharma E(1), Sharma S(2), Dharmendra S(1).

Female genital tuberculosis (FGTB) is an important cause of significant morbidity and infertility. Gold-standard diagnosis by demonstration of acid fast bacilli on microscopy or culture or detection of epithelioid granuloma on histopathology of endometrial or peritoneal biopsy is positive in only small percentage of cases due to its paucibacillary nature. Use of gene Xpert on endometrial or peritoneal biopsy has improved sensitivity of diagnosis. Composite reference standard (CRS) is a significant landmark in its diagnosis in which combination of factors like AFB on microscopy or culture, positive gene Xpert, epithelioid granuloma on endometrial or peritoneal biopsy, demonstration of definite or probable findings of FGTB on laparoscopy or hysteroscopy. There have been many advances and changes in management of FGTB recently. The program is now called National Tuberculosis Elimination Program (NTEP), and categorization of TB has been stopped. Now, patients are divided into drug-sensitive FGTB for which rifampicin (R), isoniazid (H), pyrazinamide (Z) and ethambutol (E) are given orally daily for 2 months followed by three drugs (rifampicin, isoniazid and ethambutol (RHE) orally daily for next 4 months. Multi-drug-resistant FGTB is treated with shorter MDR TB regimen of 9-11 months or longer MDR TB regimen of 18-20 months with reserved drugs. In vitro fertilization and embryo transfer have good results for blocked tubes and receptive endometrium, while surrogacy or adoption is advised for severe grades of Asherman's syndrome.

DOI: 10.1007/s13224-021-01523-9
PMCID: PMC8402974
PMID: 34483510

36. **Diagnostic accuracy of the FluoroType MTB and MTBDR VER 2.0 assays for the**

centralized high-throughput detection of Mycobacterium tuberculosis complex DNA and isoniazid and rifampicin resistance.

Clin Microbiol Infect. 2021 Sep;27(9):1351.e1-1351.e4. doi: 10.1016/j.cmi.2021.04.022. Epub 2021 Apr 30.

Dippenaar A(1), Derendinger B(1), Dolby T(2), Beylis N(3), van Helden PD(1), Theron G(1), Warren RM(1), de Vos M(4).

OBJECTIVES: To evaluate the accuracy of two new molecular diagnostic tests for the detection of drug-resistant tuberculosis, the FluoroType MTB and MTBDR VER 2.0 assays, in combination with manual and automated DNA extraction methods.
METHODS: Sputa from 360 Xpert Ultra Mycobacterium tuberculosis complex (MTBC)-positive patients and 250 Xpert Ultra MTBC-negative patients were tested. GenoType MTBDRplus served as reference for MTBC and drug resistance detection. Sanger sequencing was used to resolve discrepancies.
RESULTS: FluoroType MTB VER 2.0 showed similar MTBC sensitivity compared with FluoroType MTBDR VER 2.0 (manual DNA extraction: 91.6% (294/321) versus 89.8% (291/324); p 0.4); automated DNA extraction: 92.1% (305/331) versus 87.7% (291/332); p 0.05)). FluoroType MTBDR VER2.0 showed comparable diagnostic accuracy to FluoroType MTBDR VER1.0 as previously reported for the detection of MTBC and rifampicin and isoniazid resistance.
CONCLUSIONS: The FluoroType MTB and MTBDR VER 2.0 assays together with an automated DNA extraction and PCR set-up platform may improve laboratory operational efficiency for the diagnosis of MTBC and resistance to rifampicin and isoniazid and show promise for the implementation in a centralized molecular drug susceptibility testing model.

DOI: 10.1016/j.cmi.2021.04.022
PMID: 33933566

37. **Identification of active molecules against Mycobacterium tuberculosis through machine learning.**

Brief Bioinform. 2021 Sep 2;22(5):bbab068. doi: 10.1093/bib/bbab068.

Ye Q(1), Chai X(1), Jiang D(1), Yang L(1), Shen C(1), Zhang X(1), Li D(2), Cao D(3), Hou T(1).

Tuberculosis (TB) is an infectious disease caused by Mycobacterium tuberculosis (Mtb) and it has been one of the top 10 causes of death globally. Drug-resistant

tuberculosis (XDR-TB), extensively resistant to the commonly used first-line drugs, has emerged as a major challenge to TB treatment. Hence, it is quite necessary to discover novel drug candidates for TB treatment. In this study, based on different types of molecular representations, four machine learning (ML) algorithms, including support vector machine, random forest (RF), extreme gradient boosting (XGBoost) and deep neural networks (DNN), were used to develop classification models to distinguish Mtb inhibitors from noninhibitors. The results demonstrate that the XGBoost model exhibits the best prediction performance. Then, two consensus strategies were employed to integrate the predictions from multiple models. The evaluation results illustrate that the consensus model by stacking the RF, XGBoost and DNN predictions offers the best predictions with area under the receiver operating characteristic curve of 0.842 and 0.942 for the 10-fold cross-validated training set and external test set, respectively. Besides, the association between the important descriptors and the bioactivities of molecules was interpreted by using the Shapley additive explanations method. Finally, an online webserver called ChemTB (http://cadd.zju.edu.cn/chemtb/) was developed, and it offers a freely available computational tool to detect potential Mtb inhibitors.

DOI: 10.1093/bib/bbab068
PMID: 33822874

38. **A recombinant selective drug-resistant M. bovis BCG enhances the bactericidal activity of a second-line anti-tuberculosis regimen.**

Biomed Pharmacother. 2021 Aug 21;142:112047. doi: 10.1016/j.biopha.2021.112047. Online ahead of print.

Chiwala G(1), Liu Z(2), Mugweru JN(3), Wang B(4), Khan SA(5), Bate PNN(1), Yusuf B(1), Hameed HMA(1), Fang C(1), Tan Y(6), Guan P(6), Hu J(6), Tan S(6), Liu J(6), Zhong N(7), Zhang T(8).

Drug-resistant tuberculosis (DR-TB) poses a new threat to global health; to improve the treatment outcome, therapeutic vaccines are considered the best chemotherapy adjuvants. Unfortunately, there is no therapeutic vaccine approved against DR-TB. Our study assessed the therapeutic efficacy of a recombinant drug-resistant BCG (RdrBCG) vaccine in DR-TB. We constructed the RdrBCG overexpressing Ag85B and Rv2628 by selecting drug-resistant BCG strains and transformed them with plasmid pEBCG or pIBCG to create RdrBCG-E and RdrBCG-I respectively. Following successful stability testing, we tested the vaccine's

safety in severe combined immune deficient (SCID) mice that lack both T and B lymphocytes plus immunoglobulins. Finally, we evaluated the RdrBCG's therapeutic efficacy in BALB/c mice infected with rifampin-resistant M. tuberculosis and treated with a second-line anti-TB regimen. We obtained M. bovis strains which were resistant to several second-line drugs and M. tuberculosis resistant to rifampin. Notably, the exogenously inserted genes were lost in RdrBCG-E but remained stable in the RdrBCG-I both in vitro and in vivo. When administered adjunct to a second-line anti-TB regimen in a murine model of DR-TB, the RdrBCG-I lowered lung M. tuberculosis burden by 1 log10. Furthermore, vaccination with RdrBCG-I adjunct to chemotherapy minimized lung tissue pathology in mice. Most importantly, the RdrBCG-I showed almost the same virulence as its parent BCG Tice strain in SCID mice. Our findings suggested that the RdrBCG-I was stable, safe and effective as a therapeutic vaccine. Hence, the "recombinant" plus "drug-resistant" BCG strategy could be a useful concept for developing therapeutic vaccines against DR-TB.

DOI: 10.1016/j.biopha.2021.112047
PMID: 34426260

39. **Molecular Characteristics and Drug Resistance of Mycobacterium tuberculosis Isolate Circulating in Shaanxi Province, Northwestern China.**

Microb Drug Resist. 2021 Sep;27(9):1207-1217. doi: 10.1089/mdr.2020.0496. Epub 2021 Mar 31.

Yang J(1)(2), Zhang T(3), Xian X(3), Li Y(2), Wang R(2), Wang P(2), Zhang M(2), Wang J(1).

Objective: Shaanxi is the most highly populated province with high burdens of tuberculosis in northwestern China. The aim of this study was to investigate the molecular characteristics and drug resistance of Mycobacterium tuberculosis isolates from Shaanxi province of China in 2018. Methods: Phenotypic drug susceptibility testing and spoligotyping methods were performed on 518 M. tuberculosis isolates; drug-resistant isolates were sequenced in 11 drug loci, including katG, inhA, oxyR-ahpC, rpoB, embB, rpsL, rrs1 (nucleotides 388-1084), gyrA, gyrB, rrs2 (nucleotides 1158-1674), and eis. Results: The prevalences of isoniazid, rifampicin, ethambutol, streptomycin, ofloxacin, and kanamycin resistance were 22.0%, 19.3%, 7.9%, 23.8%, 10.4%, and 3.3%, respectively. The Beijing family (82.8%) was the predominant genotype, followed by the T (9.3%), H (0.6%), CAS (0.4%), LAM (0.4%), and U (0.4%) families. The percentage of Beijing

genotype in a central area (88.1%) was higher than in the south (77.3%) and the north area (80.1%) ($p < 0.05$), while the sex, age, and treatment history between Beijing and non-Beijing family were not statistically different. Mutation analysis found that the most prevalent mutations were katG315, rpoB531, embB306, rpsL43, gyrA94, and rrs1401; the Beijing family exhibited a high rate of isoniazid-resistant isolates carrying katG315 mutations ($p < 0.05$). Furthermore, compared with the phenotypic data, the sensitivities of isoniazid, rifampicin, ethambutol, streptomycin, ofloxacin, and kanamycin resistance by sequencing base on 11 loci were 85.1%, 94.0%, 53.7%, 74.8%, 77.8%, and 64.7%, respectively. Conclusions: Shaanxi has a serious epidemic of drug-resistant tuberculosis, Beijing family is the predominant genotype, and the distribution showed geographic diversity. The prevalence of Beijing genotypes has a tendency to promote the transmission of high-level isoniazid-resistant M. tuberculosis. Besides, the hot spot regions localized in the embB, rrs2, and eis gene appear not to serve as excellent biomarkers for predicting ethambutol and kanamycin resistance in Shaanxi.

DOI: 10.1089/mdr.2020.0496
PMID: 33794134

40. **Caregiver-child separation during tuberculosis hospitalisation: a qualitative study in South Africa.**

S Afr J Psychol. 2021 Sep 1;51(3):409-421. doi: 10.1177/0081246320962729. Epub 2020 Oct 12.

Meyerson KA(1), Hoddinott G(1), Garcia-Prats AJ(1), Tomlinson M(2)(3).

There are an estimated 32,000 incident cases of multidrug-resistant tuberculosis in children globally each year. Extended hospitalisation is often required to ensure optimal adherence to the complex multidrug-resistant tuberculosis treatment regimen. Hospitalisation usually results in caregiver-child separation which is known to cause psychological difficulties in children. We explored caregivers' and health workers' perceptions of the effects of caregiver-child separation during hospitalisation for tuberculosis in the Western Cape. We conducted semi-structured interviews with health workers (n = 7) and caregivers (n = 14) of children who were receiving multidrug-resistant tuberculosis treatment. All interviews were audio-recorded, transcribed, and translated. We used thematic analysis to organise and interpret the data. We identified three themes: (1) multidrug-resistant tuberculosis treatment was a distressing experience for children, caregivers, and health workers; (2) children's behavioural states during and post-hospitalisation (e.g., crying, aggression, hyperactivity, and withdrawal) were suggestive of their distress; and (3)

caregivers and health workers used strategies, such as deception, threat, and the prioritisation of biomedical health over psychological health as a means to manage their own as well as the children's distress. This article presents novel research on the dynamics involved in caregiver-child separation as a result of multidrug-resistant tuberculosis treatment in South Africa. We highlight that the challenges of caregiver-child separation intersected with predisposing factors related to the social adversity that families affected by childhood tuberculosis experience. Delivery models that facilitate outpatient community-based care should be prioritised and a more structured form of psychological support should be implemented for those who still require hospitalisation.

DOI: 10.1177/0081246320962729
PMCID: PMC8389357
PMID: 34456393

41. **Improving healthcare for patients with HIV, tuberculosis and hepatitis C in eastern Europe: a review of current challenges and important next steps.**

HIV Med. 2021 Sep 1. doi: 10.1111/hiv.13163. Online ahead of print.

Kraef C(1)(2)(3), Bentzon A(1), Skrahina A(4), Mocroft A(1)(5), Peters L(1), Lundgren JD(1)(2), Chkhartishvili N(6)(7), Podlekareva D(1)(2), Kirk O(1)(2).

OBJECTIVES: In some eastern European countries, serious challenges exist to meet the HIV-, tuberculosis (TB)- and hepatitis-related target of the United Nations Sustainable Development Goals. Some of the highest incidence rates for HIV and the highest proportion of multi-drug-resistant (MDR) tuberculosis worldwide are found in the region. The purpose of this article is to review the challenges and important next steps to improve healthcare for people living with TB, HIV and hepatitis C (HCV) in eastern Europe.
METHODS: References for this narrative review were identified through systematic searches of PubMed using pre-idientified key word for articles published in English from January 2000 to August 2020. After screening of titles and abstracts 37 articles were identified as relevant for this review. Thirty-eight further articles and sources were identified through searches in the authors' personal files and in Google Scholar.
RESULTS: Up to 50% of HIV/MDR-TB-coinfected individuals in the region die within 2 years of treatment initiation. Antiretroviral therapy (ART) coverage for people living with HIV (PLHIV) and the proportion virological suppressed are far below the UNAIDS 90% targets. In theory, access to various diagnostic tests and treatment of drug-resistant TB exists, but real-life data point towards inadequate testing and treatment. New treatments could provide elimination of

viral HCV in high-risk populations but few countries have national programmes. CONCLUSION: Some eastern European countries face serious challenges to achieve the sustainable development goal-related target of 3.3 by 2030, among others, to end the epidemics of AIDS and tuberculosis. Better integration of healthcare systems, standardization of health care, unrestricted substitution therapy for all people who inject drugs, widespread access to drug susceptibility testing, affordable medicines and a sufficiently sized, well-trained health workforce could address some of those challenges.

DOI: 10.1111/hiv.13163
PMID: 34468073

42. **Profiling and identification of novel rpoB mutations in rifampicin-resistant Mycobacterium tuberculosis clinical isolates from Pakistan.**

J Infect Chemother. 2021 Nov;27(11):1578-1583. doi: 10.1016/j.jiac.2021.06.020. Epub 2021 Jul 7.

Qadir M(1), Tahseen S(2), McHugh TD(3), Hussain A(2), Masood F(2), Ahmed N(2), Faryal R(4).

INTRODUCTION: Rifampicin (RIF) is one of the most effective anti-tuberculosis first-line drugs prescribed along with isoniazid. However, the emergence of RIF resistance Mycobacterium tuberculosis (MTB) isolates is a major issue towards tuberculosis (TB) control program in high MDR TB-burdened countries including Pakistan. Molecular data behind phenotypic resistance is essential for better management of RIF resistance which has been linked with mutations in rpoB gene. Since molecular studies on RIF resistance is limited in Pakistan, the current study was aimed to investigate the molecular data of mutations in rpoB gene behind phenotypic RIF resistance isolates in Pakistan.
METHOD: A total of 322 phenotypically RIF-resistant isolates were randomly selected from National TB Reference Laboratory, Pakistan for sequencing while 380 RIF resistance whole-genome sequencing (WGS) of Pakistani isolates (BioProject PRJEB25972), were also analyzed for rpoB mutations.
RESULT: Among the 702 RIF resistance samples, 675 (96.1%) isolates harbored mutations in rpoB in which 663 (94.4%) were detected within the Rifampicin Resistance Determining Region (RRDR) also known as a mutation hot spot region, including three novel. Among these mutations, 657 (97.3%) were substitutions including 603 (89.3%) single nucleotide polymorphism, 49 (7.25%) double and five (0.8%) triple. About 94.4% of Phenotypic RIF resistance strains, exhibited mutations in RRDR, which were also detectable by GeneXpert.

CONCLUSION: Mutations in the RRDR region of rpoB is a major mechanism of RIF resistance in MTB circulating isolates in Pakistan. Molecular detection of drug resistance is a faster and better approach than phenotypic drug susceptibility testing to reduce the time for transmission of RIF resistance strains in population. Such insights will inform the deployment of anti-TB drug regimens and disease control tools and strategies in high burden settings, such as Pakistan.

DOI: 10.1016/j.jiac.2021.06.020
PMID: 34244055 [Indexed for MEDLINE]

43. **Beijing genotype of Mycobacterium tuberculosis is associated with extensively drug-resistant tuberculosis: A global analysis.**

New Microbes New Infect. 2021 Aug 1;43:100921. doi: 10.1016/j.nmni.2021.100921. eCollection 2021 Sep.

Keikha M(1)(2), Majidzadeh M(1)(2).

We found that the frequency of Beijing genotype among XDR-TB strains was high. The data in this study would help guide the TB control program, and we however need further investigation to confirm the reliability of the present findings.

DOI: 10.1016/j.nmni.2021.100921
PMCID: PMC8383003
PMID: 34466269

44. **Epigenetic code during mycobacterial infections: therapeutic implications for tuberculosis.**

FEBS J. 2021 Aug 28. doi: 10.1111/febs.16170. Online ahead of print.

Fatima S(1), Kumari A(1), Agarwal M(2), Pahuja I(1), Yadav V(3), Dwivedi VP(1), Bhaskar A(1).

Epigenetics involves changing the gene function without any change in the sequence of the genes. In the case of tuberculosis (TB) infections, the bacilli, Mycobacterium tuberculosis (M.tb), uses epigenetics as a tool to protect itself

from the host immune system. TB is a deadly disease-causing maximum death per year due to a single infectious agent. In the case of TB, there is an urgent need for novel host-directed therapies which can effectively target the survival and long-term persistence of the bacteria without developing drug resistance in the bacterial strains while also reducing the duration and toxicity associated with the mainstream anti-TB drugs. Recent studies have suggested that TB infection has a significant effect on the host epigenome thereby manipulating the host immune response in the favor of the pathogen. M.tb alters the activation status of key genes involved in the immune response against TB to promote its survival and subvert the antibacterial strategies of the host. These changes are reversible and can be exploited to design very efficient host-directed therapies to fight against TB. This review has been written with the purpose of discussing the role of epigenetic changes in TB pathogenesis and the therapeutic approaches involving epigenetics, which can be utilized for targeting the pathogen.

DOI: 10.1111/febs.16170
PMID: 34453865

45. **Tuberculosis related disability: a systematic review and meta-analysis.**

BMC Med. 2021 Sep 9;19(1):203. doi: 10.1186/s12916-021-02063-9.

Alene KA(#)(1)(2)(3), Wangdi K(#)(3), Colquhoun S(4), Chani K(3), Islam T(5), Rahevar K(5), Morishita F(5), Byrne A(6)(7), Clark J(8), Viney K(3)(9)(10).

BACKGROUND: The sustainable development goals aim to improve health for all by 2030. They incorporate ambitious goals regarding tuberculosis (TB), which may be a significant cause of disability, yet to be quantified. Therefore, we aimed to quantify the prevalence and types of TB-related disabilities.
METHODS: We performed a systematic review of TB-related disabilities. The pooled prevalence of disabilities was calculated using the inverse variance heterogeneity model. The maps of the proportions of common types of disabilities by country income level were created.
RESULTS: We included a total of 131 studies (217,475 patients) that were conducted in 49 countries. The most common type of disabilities were mental health disorders (23.1%), respiratory impairment (20.7%), musculoskeletal impairment (17.1%), hearing impairment (14.5%), visual impairment (9.8%), renal impairment (5.7%), and neurological impairment (1.6%). The prevalence of respiratory impairment (61.2%) and mental health disorders (42.0%) was highest in low-income countries while neurological impairment was highest in lower

middle-income countries (25.6%). Drug-resistant TB was associated with respiratory (58.7%), neurological (37.2%), and hearing impairments (25.0%) and mental health disorders (26.0%), respectively.
CONCLUSIONS: TB-related disabilities were frequently reported. More uniform reporting tools for TB-related disability and further research to better quantify and mitigate it are urgently needed.
PROSPERO REGISTRATION NUMBER: CRD42019147488.

DOI: 10.1186/s12916-021-02063-9
PMCID: PMC8426113
PMID: 34496845

46. **Direct detection of resistance to fluoroquinolones/SLIDs in sputum specimen by GenoType MTBDRsl v.2.0 assay A study from Eastern Uttar Pradesh, India.**

Ann Clin Microbiol Antimicrob. 2021 Aug 26;20(1):56. doi: 10.1186/s12941-021-00463-6.

Singh K(1), Kumari R(1), Gupta S(1), Tripathi R(1), Srivastava A(1), Shakya V(2), Gupta A(3), Anupurba S(4).

BACKGROUND: According to World Health Organization (WHO), drug-resistant tuberculosis (DR-TB) is a major contributor to antimicrobial resistance globally and continues to be a public health threat. Annually, about half a million people fall ill with DR-TB globally. The gradual increase in resistance to fluoroquinolones (FQs) and second-line injectable drugs (SLIDs), poses a serious threat to effective TB control and adequate patient management. Therefore, WHO suggests the use of GenoType MTBDRsl v.2.0 assay for detection of multiple mutations associated with FQs and SLIDs. Hence, the study was conducted to determine the prevalence of resistance to FQs and SLIDs by comparing direct GenoType MTBDRsl v.2.0 assay with phenotypic drug susceptibility testing (DST).
METHODS: The study was conducted on 1320 smear positive sputum samples from a total of 2536 RR-TB, confirmed by GeneXpert MTB/RIF. The smear positive specimens were decontaminated, and DNA extraction was performed. Furthermore, the extracted DNA was used for GenoType MTBDRsl v.2.0 assay. While 20% of the decontaminated specimens were inoculated in Mycobacterium growth indicator tube (MGIT) for drug susceptibility testing (DST).
RESULTS: Out of 1320 smear positive sputum samples, 1178 were identified as Mycobacterium tuberculosis complex (MTBC) and remaining were negative by GenoType MTBDRsl v.2.0 assay. Of the 1178 MTBC positive, 26.6% were sensitive to both FQs and SLIDs, whereas 57.3% were only FQs resistant and 15.9% were

resistant to both FQs and SLIDs. Further DST of 225 isolates by liquid culture showed that 17% were sensitive to both FQs and SLIDs, 61.3% were only FQs resistant and 21.3% were resistant to both. The specificity for FQs and SLIDs was 92.31% and 100% whereas sensitivity was 100% respectively by GenoType MTBDRsl v.2.0 assay in direct sputum samples.
CONCLUSIONS: Our study clearly suggests that GenoType MTBDRsl v.2.0 assay is a reliable test for the rapid detection of resistance to second-line drugs after confirmation by GeneXpert MTB/RIF assay for RR-TB. Though, high rate FQ (ofloxacin) resistance was seen in our setting, moxifloxacin could be used as treatment option owing to very low resistance.

DOI: 10.1186/s12941-021-00463-6
PMCID: PMC8394194
PMID: 34446022

47. **Local Transmission Plays No Important Role in the Occurrence of Multidrug-Resistant Tuberculosis in Immigrants to Canada: An In-depth Epidemiologic Analysis.**

J Infect Dis. 2021 Sep 17;224(6):1029-1038. doi: 10.1093/infdis/jiab045.

Long R(1), Lau A(1), Egedahl ML(1), Paulsen C(1), Heffernan C(1), Edwards B(2), Cooper R(1).

BACKGROUND: Multidrug-resistant (MDR) tuberculosis has increased among migrants in Canada. The cause(s) of this increase is unknown.
METHODS: We performed a retrospective cohort study in a Canadian province with substantially increased immigration between 1982-2001 and 2002-2019. The proportion of MDR tuberculosis among migrants arriving from high MDR (HMDR) tuberculosis burden countries during these 2 periods was used to estimate the proportion of cases due to immigration versus change in proportion in the country of birth. Epidemiologic, spatiotemporal, and drug resistance pattern data were used to confirm local transmission.
RESULTS: Fifty-two of 3514 (1.48%) foreign-born culture-positive tuberculosis patients had MDR tuberculosis: 8 (0.6%) in 1982-2001 and 44 (2.0%) in 2002-2019. Between time periods, the proportion of MDR tuberculosis among migrants with tuberculosis from HMDR tuberculosis countries increased from 1.11% to 3.62%, P = .003; 31.6% attributable to recent immigration and 68.4% to a higher proportion of MDR tuberculosis in cases arrived from HMDR tuberculosis countries. No cases of MDR tuberculosis were attributable to local transmission.
CONCLUSIONS: In stark contrast to HMDR tuberculosis countries, local

transmission plays no important role in the occurrence of MDR tuberculosis in Canada. Improved tuberculosis programming in HMDR tuberculosis countries is urgently needed.

DOI: 10.1093/infdis/jiab045
PMID: 33502538

48. **Outbreak of pre- and extensively drug-resistant tuberculosis in northern Italy: urgency of cross-border, multidimensional, surveillance systems.**

Eur Respir J. 2021 Sep 16;58(3):2100839. doi: 10.1183/13993003.00839-2021. Print 2021 Sep.

Villa S(1)(2), Tagliani E(3)(2), Borroni E(3), Castellotti PF(4), Ferrarese M(4), Ghodousi A(3), Lamberti A(5), Senatore S(5), Faccini M(5)(6), Cirillo DM(7)(6), Codecasa LR(8)(6).

DOI: 10.1183/13993003.00839-2021
PMID: 34049944

49. **Flunarizine suppresses Mycobacterium tuberculosis growth via calmodulin-dependent phagosome maturation.**

J Leukoc Biol. 2021 Sep 17. doi: 10.1002/JLB.4A0221-119RR. Online ahead of print.

Mo S(1), Liu X(2)(3), Zhang K(1)(4), Wang W(1)(4), Cai Y(1), Ouyang Q(1), Zhu C(5), Lin D(1), Wan H(2), Li D(6), Wen Z(6), Chen X(1).

Tuberculosis (TB), an infectious bacterial disease caused by Mycobacterium tuberculosis (Mtb), is a major cause of death worldwide. Multidrug-resistant TB remains a public health crisis and thus novel effective treatments, such as host-directed therapies (HDTs), are urgently required to overcome the challenges of TB infection. In this study, we evaluated 4 calcium modulators for their effects on Mtb growth in macrophages. Only flunarizine enhanced the bactericidal ability of macrophages against Mtb, which was induced by an increase in phosphorylated calcium/calmodulin (CaM)-dependent protein kinase II (pCaMKII) levels. We further discovered that the expression of CaM was decreased in

Mtb-infected macrophages and restored following flunarizine treatment; this was associated with phagolysosome maturation and acidification. Consistent with these findings, the anti-TB ability of macrophages was reduced following the silencing of CaM or inhibition of CAMKII activity. In conclusion, our results demonstrated that flunarizine enhanced the bactericidal ability of macrophages and clarified its CaM-pCAMKII-dependent mechanism. Therefore, our findings strongly support further studies of this currently approved drug as an HDT candidate for TB therapy.

DOI: 10.1002/JLB.4A0221-119RR
PMID: 34533236

50. **Current perspective of ATP synthase inhibitors in the management of the tuberculosis.**

Curr Top Med Chem. 2021 Sep 13. doi: 10.2174/1568026621666210913122346. Online ahead of print.

Divita KM(1), Khatik GL(1).

INTRODUCTION: Tuberculosis is a life-threatening disease, and the drugs discovered during the era of 1950 and 1970 are found inefficient due to emergent MDR and XDR-TB. Tuberculosis is difficult to treat due to the development of antibiotic resistance. ATP synthase is consisting of two units, F1 and F0 units. These are present in the cytoplasm and membrane of mitochondria, respectively. F1 unit comprises of a, b, and c subunit while F0 subunit has α, β, γ, δ, ε subunits. Bedaquiline is the first approved ATP synthase inhibitor in 2012 by USFDA.
METHODS: Recent literature from 2005-2020 were collected using Pubmed with the keywords ATP synthase inhibitor, bedaquiline derivatives, tuberculosis. The work describing detailed analyses of bedaquiline (BDQ) was included in the current work, and others were excluded.
RESULTS: ATP production occurs via the ATP synthase enzyme, leading to the growth and multiplication of mycobacteria. BDQ inhibits the mycobacterium ATP synthase enzyme, a heteropolymeric complex consisting of two subunits, but it does not interfere with mammalian ATP synthase. Bedaquiline (BDQ) has become a drug of choice to treat MDR-TB and help to reduce the treatment span. Recently observed triple mutation as wtLeu59A → mtVal59A; wtIle66A→ mtMet66A and wtGlu61B → mtAsp61B of ATP synthase led to decrease BDQ binding affinity; thus, researchers are putting efforts for its newer derivative discovery.
CONCLUSION: ATP synthase inhibitor could be an alternative approach for better

treatment of tuberculosis. Herein we discussed the recent advancements in the development of newer analogues of BDQ with its future perspectives.

DOI: 10.2174/1568026621666210913122346
PMID: 34517802

51. **Trends in primary multidrug-resistant tuberculosis in the State of Rio de Janeiro: a retrospective study conducted during 2000-2019.**

Rev Soc Bras Med Trop. 2021 Aug 20;54:e00862021. doi: 10.1590/0037-8682-0086-2021. eCollection 2021.

Bhering M(1)(2), Kritski A(1).

INTRODUCTION: We analyzed the trends in primary multidrug-resistant tuberculosis (MDR-TB).
METHODS: We performed a time series analysis of primary MDR-TB cases reported in the State of Rio de Janeiro (RJ) during 2000-2019. The annual percent change and the average annual percentage change (AAPC) were computed using joinpoint regression analysis.
RESULTS: The percentage of cases increased from 7.69% in 2000 to 38.42% in 2018. We observed an upward trend during this period (AAPC = 9.4; 95% confidence interval 1.4-18.0, $p < 0.001$).
CONCLUSIONS: The trend indicates the increasing occurrence of MDR-TB transmission sources in RJ during 2000-2019.

DOI: 10.1590/0037-8682-0086-2021
PMCID: PMC8405210
PMID: 34431941 [Indexed for MEDLINE]

52. **Lesion Penetration and Activity Limit the Utility of Second-Line Injectable Agents in Pulmonary Tuberculosis.**

Antimicrob Agents Chemother. 2021 Sep 17;65(10):e0050621. doi: 10.1128/AAC.00506-21. Epub 2021 Jul 12.

Ernest JP(#)(1), Sarathy J(#)(2), Wang N(2), Kaya F(2), Zimmerman MD(2), Strydom N(1), Wang H(2), Xie M(2), Gengenbacher M(2)(3), Via LE(4)(5), Barry CE 3rd(4)(5), Carter CL(2), Savic RM(1), Dartois V(2)(3).

Amikacin and kanamycin are second-line injectables used in the treatment of multidrug-resistant tuberculosis (MDR-TB) based on the clinical utility of streptomycin, another aminoglycoside and first-line anti-TB drug. While streptomycin was tested as a single agent in the first controlled TB clinical trial, introduction of amikacin and kanamycin into MDR-TB regimens was not preceded by randomized controlled trials. A recent large retrospective meta-analysis revealed that compared with regimens without any injectable drug, amikacin provided modest benefits, and kanamycin was associated with worse outcomes. Although their long-term use can cause irreversible ototoxicity, they remain part of MDR-TB regimens because they have a role in preventing emergence of resistance to other drugs. To quantify the contribution of amikacin and kanamycin to second-line regimens, we applied two-dimensional matrix-assisted laser desorption ionization (MALDI) mass spectrometry imaging in large lung lesions, quantified drug exposure in lung and in lesions of rabbits with active TB, and measured the concentrations required to kill or inhibit growth of the resident bacterial populations. Using these metrics, we applied site-of-action pharmacokinetic and pharmacodynamic (PK-PD) concepts and simulated drug coverage in patients' lung lesions. The results provide a pharmacological explanation for the limited clinical utility of both agents and reveal better PK-PD lesion coverage for amikacin than kanamycin, consistent with retrospective data of contribution to treatment success. Together with recent mechanistic studies dissecting antibacterial activity from aminoglycoside ototoxicity, the limited but rapid penetration of streptomycin, amikacin, and kanamycin to the sites of TB disease supports the development of analogs with improved efficacy and tolerability.

DOI: 10.1128/AAC.00506-21
PMID: 34252307

53. **Population pharmacokinetics and pharmacodynamics of investigational regimens' drugs in the TB-PRACTECAL clinical trial (the PRACTECAL-PKPD study): a prospective nested study protocol in a randomised controlled trial.**

BMJ Open. 2021 Sep 6;11(9):e047185. doi: 10.1136/bmjopen-2020-047185.

Nyang'wa BT(1)(2), Kloprogge F(3), Moore DAJ(2), Bustinduy A(2), Motta I(4), Berry C(4), Davies GR(5).

INTRODUCTION: Drug-resistant tuberculosis (TB) remains a global health threat, with little over 50% of patients successfully treated. Novel regimens like the ones being studied in the TB-PRACTECAL trial are urgently needed. Understanding anti-TB drug exposures could explain the success or failure of these trial

regimens. We aim to study the relationship between the patients' exposure to anti-TB drugs in TB-PRACTECAL investigational regimens and their treatment outcomes.
METHODS AND ANALYSIS: Adults with multidrug-resistant TB randomised to investigational regimens in TB-PRACTECAL will be recruited to a nested pharmacokinetic-pharmacodynamic (PKPD) study. Venous blood samples will be collected at 0, 2 and 23 hours postdose on day 1 and 0, 6.5 and 23 hours postdose during week 8 to quantify drug concentrations in plasma. Trough samples will be collected during week 12, 16, 20 and 24 visits. Opportunistic samples will be collected during weeks 32 and 72. Drug concentrations will be quantified using liquid chromatography-tandem mass spectrometry. Sputum samples will be collected at baseline, monthly to week 24 and then every 2 months to week 108 for MICs and bacillary load quantification. Full blood count, urea and electrolytes, liver function tests, lipase, ECGs and ophthalmology examinations will be conducted at least monthly during treatment.PK and PKPD models will be developed for each drug with nonlinear mixed effects methods. Optimal dosing will be investigated using Monte-Carlo simulations.
ETHICS AND DISSEMINATION: The study has been approved by the Médecins sans Frontières (MSF) Ethics Review Board, the LSHTM Ethics Committee, the Belarus RSPCPT ethics committee and PharmaEthics and the University of Witwatersrand Human Research ethics committee in South Africa. Written informed consent will be obtained from all participants. The study results will be shared with public health authorities, presented at scientific conferences and published in a peer-reviewed journal.
TRIAL REGISTRATION NUMBER: NCT04081077; Pre-results.

DOI: 10.1136/bmjopen-2020-047185
PMID: 34489274 [Indexed for MEDLINE]

54. **Tuberculosis preventive therapy for people living with HIV: A systematic review and network meta-analysis.**

PLoS Med. 2021 Sep 14;18(9):e1003738. doi: 10.1371/journal.pmed.1003738. eCollection 2021 Sep.

Yanes-Lane M(1), Ortiz-Brizuela E(1)(2), Campbell JR(1)(3), Benedetti A(1)(3)(4), Churchyard G(5)(6), Oxlade O(1), Menzies D(1)(3).

Comment in
Tuberculosis preventive treatment in people living with HIV - is the glass

half empty, or half full?

Economic and modelling evidence for tuberculosis preventive therapy among people living with HIV: a systematic review & meta-analysis.

The Latent Tuberculosis Cascade-of-Care Among People Living with HIV: A Systematic Review and Meta-Analysis.

BACKGROUND: Tuberculosis (TB) preventive therapy (TPT) is an essential component of care for people living with HIV (PLHIV). We compared efficacy, safety, completion, and drug-resistant TB risk for currently recommended TPT regimens through a systematic review and network meta-analysis (NMA) of randomized trials.

METHODS AND FINDINGS: We searched MEDLINE, Embase, and the Cochrane Library from inception through June 9, 2020 for randomized controlled trials (RCTs) comparing 2 or more TPT regimens (or placebo/no treatment) in PLHIV. Two independent reviewers evaluated eligibility, extracted data, and assessed the risk of bias. We grouped TPT strategies as follows: placebo/no treatment, 6 to 12 months of isoniazid, 24 to 72 months of isoniazid, and rifamycin-containing regimens. A frequentist NMA (using graph theory) was carried out for the outcomes of development of TB disease, all-cause mortality, and grade 3 or worse hepatotoxicity. For other outcomes, graphical descriptions or traditional pairwise meta-analyses were carried out as appropriate. The potential role of confounding variables for TB disease and all-cause mortality was assessed through stratified analyses. A total of 6,466 unique studies were screened, and 157 full texts were assessed for eligibility. Of these, 20 studies (reporting 16 randomized trials) were included. The median sample size was 616 (interquartile range [IQR], 317 to 1,892). Eight were conducted in Africa, 3 in Europe, 3 in the Americas, and 2 included sites in multiple continents. According to the NMA, 6 to 12 months of isoniazid were no more efficacious in preventing microbiologically confirmed TB than rifamycin-containing regimens (incidence rate ratio [IRR] 1.0, 95% CI 0.8 to 1.4, p = 0.8); however, 6 to 12 months of isoniazid were associated with a higher incidence of all-cause mortality (IRR 1.6, 95% CI 1.2 to 2.0, p = 0.02) and a higher risk of grade 3 or higher hepatotoxicity (risk difference [RD] 8.9, 95% CI 2.8 to 14.9, p = 0.004). Finally, shorter regimens were associated with higher completion rates relative to longer regimens, and we did not find statistically significant differences in the risk of drug-resistant TB between regimens. Study limitations include potential confounding due to differences in posttreatment follow-up time and TB incidence in the study setting on the estimates of incidence of TB or all-cause mortality, as well as an underrepresentation of pregnant women and children.

CONCLUSIONS: Rifamycin-containing regimens appear safer and at least as effective as isoniazid regimens in preventing TB and death and should be considered part of routine care in PLHIV. Knowledge gaps remain as to which specific rifamycin-containing regimen provides the optimal balance of efficacy, completion, and safety.

DOI: 10.1371/journal.pmed.1003738
PMCID: PMC8439495
PMID: 34520459

55. **Childhood Intra-Thoracic Tuberculosis Clinical Presentation Determines Yield of Laboratory Diagnostic Assays.**

Front Pediatr. 2021 Aug 25;9:667726. doi: 10.3389/fped.2021.667726. eCollection 2021.

Singh UB(1), Verma Y(1), Jain R(2), Mukherjee A(2), Gautam H(1), Lodha R(2), Kabra SK(2).

Diagnosis of intra-thoracic tuberculosis (ITTB) in children is difficult due to the paucibacillary nature of the disease, the challenge in collecting appropriate specimens, and the low sensitivity of smear microscopy and culture. Culture and Xpert MTB/RIF provide higher diagnostic yield in presumptive TB in adults than in children. Current study was designed to understand poor yield of diagnostic assays in children. Children with presumptive ITTB were subjected to gastric aspirates and induced sputum twice. Samples were tested by Ziehl-Neelsen stain, Xpert MTB/RIF-assay, and MGIT-960 culture. Subjects were grouped as Confirmed, Unconfirmed, and Unlikely TB, and classified as progressive primary disease (PPD, lung parenchymal lesion), and primary pulmonary complex (PPC, hilar lymphadenopathy) on chest X-ray. Of children with culture-positive TB 51/394 (12.9%), culture-negative TB 305 (77.4%), and unlikely TB 38 (9.6%), 9 (2.3%) were smear positive, while 95 (24.1%) were Xpert-MTB/RIF positive. Xpert-MTB/RIF detected 40/51 culture confirmed cases (sensitivity 78.4% and NPV 96.3%). Culture was positive in more children presenting as PPD ($p < 0.04$). In culture-negative TB group, Xpert positivity was seen in 31% of those with PPD and 11.9% in those with PPC ($p < 0.001$). Conclusion: Xpert-MTB/RIF improved diagnosis by 2-fold and increased detection of MDR-TB. Both liquid culture and Xpert-MTB/RIF gave higher yield in children with lung parenchymal lesions. Children with hilar lymphadenopathy without active lung parenchymal lesions had poor diagnostic yield even with sensitive nucleic acid amplification tests, due to paucibacillary/localized disease, suggesting possible utility of invasively collected samples in early diagnosis and treatment.

DOI: 10.3389/fped.2021.667726
PMCID: PMC8425475
PMID: 34513756

56. **GenTB: A user-friendly genome-based predictor for tuberculosis resistance powered by machine learning.**

Genome Med. 2021 Aug 30;13(1):138. doi: 10.1186/s13073-021-00953-4.

Gröschel MI(1), Owens M(1), Freschi L(1), Vargas R Jr(1)(2), Marin MG(1)(2), Phelan J(3), Iqbal Z(4), Dixit A(1)(5), Farhat MR(6)(7).

BACKGROUND: Multidrug-resistant Mycobacterium tuberculosis (Mtb) is a significant global public health threat. Genotypic resistance prediction from Mtb DNA sequences offers an alternative to laboratory-based drug-susceptibility testing. User-friendly and accurate resistance prediction tools are needed to enable public health and clinical practitioners to rapidly diagnose resistance and inform treatment regimens.
RESULTS: We present Translational Genomics platform for Tuberculosis (GenTB), a free and open web-based application to predict antibiotic resistance from next-generation sequence data. The user can choose between two potential predictors, a Random Forest (RF) classifier and a Wide and Deep Neural Network (WDNN) to predict phenotypic resistance to 13 and 10 anti-tuberculosis drugs, respectively. We benchmark GenTB's predictive performance along with leading TB resistance prediction tools (Mykrobe and TB-Profiler) using a ground truth dataset of 20,408 isolates with laboratory-based drug susceptibility data. All four tools reliably predicted resistance to first-line tuberculosis drugs but had varying performance for second-line drugs. The mean sensitivities for GenTB-RF and GenTB-WDNN across the nine shared drugs were 77.6% (95% CI 76.6-78.5%) and 75.4% (95% CI 74.5-76.4%), respectively, and marginally higher than the sensitivities of TB-Profiler at 74.4% (95% CI 73.4-75.3%) and Mykrobe at 71.9% (95% CI 70.9-72.9%). The higher sensitivities were at an expense of ≤ 1.5% lower specificity: Mykrobe 97.6% (95% CI 97.5-97.7%), TB-Profiler 96.9% (95% CI 96.7 to 97.0%), GenTB-WDNN 96.2% (95% CI 96.0 to 96.4%), and GenTB-RF 96.1% (95% CI 96.0 to 96.3%). Averaged across the four tools, genotypic resistance sensitivity was 11% and 9% lower for isoniazid and rifampicin respectively, on isolates sequenced at low depth (< 10× across 95% of the genome) emphasizing the need to quality control input sequence data before prediction. We discuss differences between tools in reporting results to the user including variants underlying the resistance calls and any novel or indeterminate variants CONCLUSIONS: GenTB is an easy-to-use online tool to rapidly and accurately predict resistance to anti-tuberculosis drugs. GenTB can be accessed online at https://gentb.hms.harvard.edu , and the source code is available at https://github.com/farhat-lab/gentb-site .

DOI: 10.1186/s13073-021-00953-4
PMCID: PMC8407037
PMID: 34461978

57. **Transmission patterns of rifampicin resistant Mycobacterium tuberculosis complex strains in Cameroon: a genomic epidemiological study.**

BMC Infect Dis. 2021 Aug 31;21(1):891. doi: 10.1186/s12879-021-06593-8.

Merker M(1)(2)(3), Egbe NF(4)(5), Ngangue YR(4), Vuchas C(4), Kohl TA(6), Dreyer V(6), Kuaban C(7), Noeske J(8), Niemann S(#)(6)(9), Sander MS(#)(4).

BACKGROUND: Determining factors affecting the transmission of rifampicin (RR) and multidrug-resistant (MDR) Mycobacterium tuberculosis complex strains under standardized tuberculosis (TB) treatment is key to control TB and prevent the evolution of drug resistance.
METHODS: We combined bacterial whole genome sequencing (WGS) and epidemiological investigations for 37% (n = 195) of all RR/MDR-TB patients in Cameroon (2012-2015) to identify factors associated with recent transmission.
RESULTS: Patients infected with a strain resistant to high-dose isoniazid, and ethambutol had 7.4 (95% CI 2.6-21.4), and 2.4 (95% CI 1.2-4.8) times increased odds of being in a WGS-cluster, a surrogate for recent transmission. Furthermore, age between 30 and 50 was positively correlated with recent transmission (adjusted OR 3.8, 95% CI 1.3-11.4). We found high drug-resistance proportions against three drugs used in the short standardized MDR-TB regimen in Cameroon, i.e. high-dose isoniazid (77.4%), ethambutol (56.9%), and pyrazinamide (43.1%). Virtually all strains were susceptible to fluoroquinolones, kanamycin, and clofazimine, and treatment outcomes were mostly favourable (87.5%).
CONCLUSION: Pre-existing resistance to high-dose isoniazid, and ethambutol is associated with recent transmission of RR/MDR strains in our study. A possible contributing factor for this observation is the absence of universal drug susceptibility testing in Cameroon, likely resulting in prolonged exposure of new RR/MDR-TB patients to sub-optimal or failing first-line drug regimens.

DOI: 10.1186/s12879-021-06593-8
PMCID: PMC8406724
PMID: 34465301

58. **Computational identification and characterization of antigenic properties of Rv3899c of Mycobacterium tuberculosis and its interaction with human leukocyte antigen (HLA).**

Immunogenetics. 2021 Oct;73(5):357-368. doi: 10.1007/s00251-021-01220-x. Epub 2021 Jul 6.

Das R(1), Eniyan K(2)(3), Bajpai U(4).

A rise in drug-resistant tuberculosis (TB) cases demands continued efforts towards the discovery and development of drugs and vaccines. Secretory proteins of Mycobacterium tuberculosis (H37Rv) are frequently studied for their antigenicity and their scope as protein subunit vaccines requires further analysis. In this study, Rv3899c of H37Rv emerges as a potential vaccine candidate on its evaluation by several bioinformatics tools. It is a non-toxic, secretory protein with an 'immunoglobulin-like' fold which does not show similarity with a human protein. Through BlastP and MEME suite analysis, we found Rv3899c homologs in several mycobacterial species and its antigenic score (0.54) to compare well with the known immunogens such as ESAT-6 (0.56) and Rv1860 (0.52). Structural examination of Rv3899c predicted ten antigenic peptides, an accessibility profile of the antigenic determinants constituting B cell epitope-rich regions and a low abundance of antigenic regions (AAR) value. Significantly, STRING analysis showed ESX-2 secretion system proteins and antigenic PE/PPE proteins of H37Rv as the interacting partners of Rv3899c. Further, molecular docking predicted Rv3899c to interact with human leukocyte antigen HLA-DRB1*04:01 through its antigenically conserved motif (RAAEQQRLQRIVDAVARQEPRISWAAGLRDDGTT). Interestingly, the binding affinity was observed to increase on citrullination of its Arg1 residue. Taken together, the computational characterization and predictive information suggest Rv3899c to be a promising TB vaccine candidate, which should be validated experimentally.

DOI: 10.1007/s00251-021-01220-x
PMID: 34228167

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

BJOG. 2021 Sep 7. doi: 10.1111/1471-0528.16873. Online ahead of print.

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

DOI: 10.1111/1471-0528.16873
PMID: 34490969

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

BJOG. 2021 Sep 15. doi: 10.1111/1471-0528.16872. Online ahead of print.

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

DOI: 10.1111/1471-0528.16872
PMID: 34524715

61. **In vitro activity of bedaquiline and imipenem against actively growing, nutrient-starved, and intracellular Mycobacterium abscessus.**

Antimicrob Agents Chemother. 2021 Sep 13:AAC0154521. doi: 10.1128/AAC.01545-21. Online ahead of print.

Martins O(1), Lee J(1), Kaushik A(1), Ammerman NC(1)(2), Dooley KE(1), Nuermberger EL(1).

Mycobacterium abscessus lung disease is difficult to treat due to intrinsic drug resistance and the persistence of drug-tolerant bacteria. Currently, the standard of care is a multi-drug regimen with at least 3 active drugs, preferably including a β-lactam (imipenem or cefoxitin). These regimens are lengthy, toxic, and have limited efficacy. The search for more efficacious regimens led us to evaluate bedaquiline, a diarylquinoline licensed for treatment of multidrug-resistant tuberculosis. We performed in vitro time-kill experiments to evaluate the activity of bedaquiline alone and in combination with the first-line drug imipenem against M. abscessus under various conditions. Against actively growing bacteria, bedaquiline was largely bacteriostatic and antagonized the bactericidal activity of imipenem. Contrarily, against nutrient-starved persisters, bedaquiline was bactericidal, while imipenem was not, and bedaquiline drove the activity of the combination. In an intracellular infection model, bedaquiline and imipenem had additive bactericidal effects. Correlations between ATP levels and the bactericidal activity of imipenem and its antagonism by bedaquiline were observed. Interestingly, the presence of

Tween 80 in the media affected the activity of both drugs, enhancing the activity of imipenem and reducing that of bedaquiline. Overall, these results show that bedaquiline and imipenem interact differently depending on culture conditions. Previously reported antagonistic effects of bedaquiline on imipenem were limited to conditions with actively multiplying bacteria and/or the presence of Tween 80, whereas the combination was additive or indifferent against nutrient-starved and intracellular M. abscessus, where promising bactericidal activity of the combination suggests it may have a role in future treatment regimens.

DOI: 10.1128/AAC.01545-21
PMID: 34516254

62. **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.

DOI: 10.1016/j.ejmech.2021.113568
PMID: 34118719 [Indexed for MEDLINE]

63. **Design and synthesis of 2-(2-isonicotinoylhydrazineylidene)propanamides as InhA inhibitors with high antitubercular activity.**

Eur J Med Chem. 2021 Nov 5;223:113668. doi: 10.1016/j.ejmech.2021.113668. Epub 2021 Jun 23.

Pflégr V(1), Horváth L(2), Stolaříková J(3), Pál A(4), Korduláková J(4), Bősze S(2), Vinšová J(1), Krátký M(5).

Based on successful antitubercular isoniazid scaffold we have designed its "mee-too" analogues by a combination of this drug linked with substituted anilines through pyruvic acid as a bridge. Lipophilicity important for passive diffusion through impenetrable mycobacterial cell wall was increased by halogen substitution on the aniline. We prepared twenty new 2-(2-isonicotinoylhydrazineylidene)propanamides that were assayed against susceptible Mycobacterium tuberculosis H37Rv, nontuberculous mycobacteria, and also multidrug-resistant tuberculous strains (MDR-TB). All the compounds showed excellent activity not only against Mtb. (minimum inhibitory concentrations, MIC, from ≤0.03 μM), but also against M. kansasii (MIC ≥2 μM). The most active molecules have CF3 and OCF3 substituent in the position 4 on the aniline ring. MIC against MDR-TB were from 8 μM. The most effective derivatives were used for the mechanism of action investigation. The treatment of Mtb. H37Ra with tested compounds led to decreased production of mycolic acids and the strains overproducing InhA were more resistant to them. These results confirm that studied compounds inhibit the enoyl-acyl carrier protein reductase (InhA) in mycobacteria. The compounds did not show any cytotoxic and cytostatic activity for HepG2 cells. The amides can be considered as a promising scaffold for antitubercular drug discovery having better antimicrobial properties than original isoniazid together with a significantly improved pharmaco-toxicological profile.

DOI: 10.1016/j.ejmech.2021.113668
PMID: 34198149

64. **Comparison of different diagnostic modalities for isolation of Mycobacterium Tuberculosis among suspected tuberculous lymphadenitis patients.**

Braz J Biol. 2021 Aug 20;83:e244311. doi: 10.1590/1519-6984.244311. eCollection 2021.

Sharif N(1), Ahmed D(1), Mahmood RT(2), Qasim Z(3), Khan SN(1), Jabbar A(1), Khattak AA(1), Asad MJ(4), Ahmed W(5), Khan MM(5), Awan UA(1), Zaman N(6), Habiba U(7), Noureen S(7), Alghamdi HA(8).

Tuberculosis is a communicable disease with high morbidity and mortality rates in developing countries. The study's primary objective is to compare conventional methods such as acid-fast bacillus (AFB) culture and microscopy with rapid diagnostic methods. The secondary objective is to compare histopathological and microbiological findings in suspected patients with tubercular lymphadenitis. A total of 111 samples (August 2018 to September 2019) of lymph nodes were processed for AFB microscopy, AFB cultures, drug-susceptibility testing (DST), histopathology, and Xpert Mycobacterium Tuberculosis (MTB)/resistance to Rifampin (RIF) assays. Out of 111 lymph node samples, 6 (5.4%) were positive for AFB smear microscopy, 84 (75.6%) were positive for AFB culture, 80 (70.7%) were positive on Gene Xpert, and 102 (91.8%) were indicative of tuberculosis for histopathology studies. Mycobacteria growth indicator tube (MGIT) culture positivity was 84 (75.6%) higher than solid Lowenstein-Jensen (LJ) culture 74 (66.6%). Positive cultures underwent phenotypic DST. Two cases were Multidrug-resistant (MDR) on DST, while three cases were Rifampicin resistant on Gene Xpert. The sensitivity of Genexpert was (62%) against the conventional AFB culture method. The poor performance of conventional lymphadenitis diagnostic methods requires early and accurate diagnostic methodology. Xpert MTB/RIF test can help in the treatment of multidrug-resistant TB cases. Nonetheless, rapid and conventional methods should be used for complete isolation of Mycobacterium tuberculosis.

DOI: 10.1590/1519-6984.244311
PMID: 34431905 [Indexed for MEDLINE]

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

Comput Biol Med. 2021 Sep;136:104694. doi: 10.1016/j.compbiomed.2021.104694. Epub 2021 Jul 28.

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.

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

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

Microbiol Spectr. 2021 Sep 3;9(1):e0001921. doi: 10.1128/Spectrum.00019-21. Epub 2021 Jul 21.

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

67. **Analysis of the application of a gene chip method for detecting Mycobacterium tuberculosis drug resistance in clinical specimens: a retrospective study.**

Sci Rep. 2021 Sep 9;11(1):17951. doi: 10.1038/s41598-021-97559-y.

Feng G(#)(1), Han W(#)(2), Shi J(#)(3), Xia R(#)(3), Xu J(#)(3).

Most Mycobacterium tuberculosis (Mtb) resistant to rifampicin (RIF) has mutations in the rpoB gene, while most Mtb resistant to isoniazid (INH) has mutations in the katG gene or inhA promoter. We used gene chip technology to detect mutations in these genes to determine the resistance of Mtb to RIF and INH. A total of 4148 clinical specimens with sputum smear positivity for acid-fast bacilli (AFB) were detected. Then, taking the results of the drug

sensitivity test (DST) as the reference standard, the detection efficiency of sputum samples from different grades of positive smears was compared in detail. We found that the sensitivity of the gene chip method for detecting sputum samples with a grade ≥ AFB 2 + was higher than that of sputum samples with a grade ≤ AFB 1 + ($P < 0.05$). When the grade of the sample was ≤ AFB 1 +, the sensitivity of the gene chip method was 72.6% for RIF, 67.3% for INH, and 60.0% for MDR-TB. When the grade of the sample was ≥ AFB 2 +, the sensitivity of the gene chip method was 84.5% for RIF, 78.2% for INH, and 73.9% for MDR-TB. The results show that gene chip technology can be directly used to diagnose drug-resistant tuberculosis in clinical specimens, and the diagnostic efficiency for the detection of sputum specimens with a grade ≥ AFB 2 + is better than that of other sputum specimens.

DOI: 10.1038/s41598-021-97559-y
PMCID: PMC8429459
PMID: 34504243

68. **Insights into the mutations leading to capreomycin resistance in S-adenosyl-L-methionine binding motif in TlyA from Mycobacterium tuberculosis.**

J Biomol Struct Dyn. 2021 Aug 31:1-9. doi: 10.1080/07391102.2021.1969284. Online ahead of print.

Ali W(1), Jamal S(1), Grover A(2), Grover S(1).

Capreomycin is a second line antibiotic used for the treatment of drug resistant Tuberculosis (TB), primary reason of death from a solo infectious organism, Mycobacterium tuberculosis (M.tb). Capreomycin targets the ribosome of bacteria and is known to bind at the interface where the large and small ribosomal subunits interact in M.tb using an S-Adenosyl Methionine (SAM) dependent methyltransferase, TlyA (Rv1794). Besides the methyltransferase activity, TlyA has also been found to show substantial haemolytic activity. The dual activity of TlyA highlights its crucial role in pathogenesis and virulence of M.tb. In the present study, docking and molecular dynamics (MD) simulations were carried out to explore the impact of mutations in a conserved SAM binding motif, 90GASTG94, on the affinity of TlyA enzyme for SAM. Two already reported mutations, A91E and S92L, and the remaining wild type residues, Gly90, Thr93, Gly94 mutated to alanine were taken into consideration resulting in a total of six systems, wild type + SAM, G90A + SAM, A91E + SAM, S92L + SAM, T93A + SAM and G94A + SAM that were subjected to 100 ns MD simulations. Docking scores and MD simulations analyses revealed that in contrast to wild type, mutants reduced the

affinity of SAM for TlyA with most prominent effect observed in case of alanine mutants. Mutations also led to the loss of hydrogen bond and hydrophobic interactions and large-scale movement of atoms evident from the principal component analyses indicating their destabilizing impact on TlyA. The present study gives insights into influence of mutations on binding of SAM to TlyA in M.tb and promoting capreomycin resistance.Communicated by Ramaswamy H. Sarma.

DOI: 10.1080/07391102.2021.1969284
PMID: 34463210

69. **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.

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

70. **Treatment Outcomes of Patients with Multidrug-resistant Tuberculosis: Concern to Bedaquiline - Authors' reply.**

Tuberc Respir Dis (Seoul). 2021 Sep 13. doi: 10.4046/trd.2021.0135. Online ahead of print.

Kang Y(1), Mok J(2)(3)(4).

DOI: 10.4046/trd.2021.0135
PMID: 34510868

71. **iAtbP-Hyb-EnC: Prediction of antitubercular peptides via heterogeneous feature representation and genetic algorithm based ensemble learning model.**

Comput Biol Med. 2021 Aug 25;137:104778. doi: 10.1016/j.compbiomed.2021.104778. Online ahead of print.

Akbar S(1), Ahmad A(2), Hayat M(3), Rehman AU(4), Khan S(5), Ali F(6).

Tuberculosis (TB) is a worldwide illness caused by the bacteria Mycobacterium tuberculosis. Owing to the high prevalence of multidrug-resistant tuberculosis, numerous traditional strategies for developing novel alternative therapies have been presented. The effectiveness and dependability of these procedures are not always consistent. Peptide-based therapy has recently been regarded as a preferable alternative due to its excellent selectivity in targeting specific cells without affecting the normal cells. However, due to the rapid growth of the peptide samples, predicting TB accurately has become a challenging task. To effectively identify antitubercular peptides, an intelligent and reliable prediction model is indispensable. An ensemble learning approach was used in this study to improve expected results by compensating for the shortcomings of individual classification algorithms. Initially, three distinct representation approaches were used to formulate the training samples: k-space amino acid composition, composite physiochemical properties, and one-hot encoding. The feature vectors of the applied feature extraction methods are then combined to generate a heterogeneous vector. Finally, utilizing individual and heterogeneous vectors, five distinct nature classification models were used to evaluate prediction rates. In addition, a genetic algorithm-based ensemble model was used to improve the suggested model's prediction and training capabilities. Using Training and independent datasets, the proposed ensemble model achieved an accuracy of 94.47% and 92.68%, respectively. It was observed that our proposed "iAtbP-Hyb-EnC" model outperformed and reported ~10% highest training accuracy than existing predictors. The "iAtbP-Hyb-EnC" model is suggested to be a reliable tool for scientists and might play a valuable role in academic research and drug discovery. The source code and all datasets are publicly available at https://github.com/Farman335/iAtbP-Hyb-EnC.

DOI: 10.1016/j.compbiomed.2021.104778
PMID: 34481183

72. **Conventional and microwave-assisted organic synthesis of novel antimycobacterial agents bearing furan and pyridine hybrids.**

Drug Dev Res. 2021 Aug 20. doi: 10.1002/ddr.21872. Online ahead of print.

Desai NC(1), Bhatt K(1), Jadeja DJ(1), Mehta HK(1), Khedkar VM(2), Sarkar D(3).

Drug resistance in tuberculosis poses a serious threat to humanity because currently available antitubercular drugs are ineffective against Mycobacterium tuberculosis (M. tuberculosis). As a result, the approval of Bedaquiline and Delamanid for the treatment of drug-resistant tuberculosis was accelerated. Still, there is an urgent need to search for new antitubercular drugs with novel mechanisms of action (MoA). Due to this, we have designed a synthetic strategy by utilizing microwave-assisted organic synthesis. We have compared our method with the conventional procedure, and the data show that our procedure is more effective in the preparation of title compounds. A unique series of 1-(2-(furan-2-yl)-5-(pyridin-4-yl)-1,3,4-oxadiazol-3(2H)-yl)-3-(aryl)-prop-2-en-1-ones (5a-o) was synthesized utilizing conventional and microwave-assisted techniques. Synthetic compounds were investigated for antitubercular activity against Mycobacterium TB H37 Ra and Mycobacterium bovis (M. bovis). Compound 5b was reported to be the most effective against M. tuberculosis H37 Ra (97.69 percent inhibition at 30 μg/ml) and M. bovis (97.09 percent inhibition at 30 μg/ml). An in silico binding affinity study of mycobacterial enoyl-acyl carrier protein reductase (InhA) reveals the binding mechanism and thermodynamic interactions that determine these molecule's binding affinity. Compound 5b had a high glide score of -8.991 and low glide energy of -49.893 kcal/mol.

DOI: 10.1002/ddr.21872
PMID: 34414591

73. **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.

DOI: 10.1016/j.ejmech.2021.113603
PMID: 34126456 [Indexed for MEDLINE]

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

Future Microbiol. 2021 Sep;16:949-953. doi: 10.2217/fmb-2021-0032. Epub 2021 Aug 13.

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.

DOI: 10.2217/fmb-2021-0032
PMID: 34384261