May Literature

1. An All-Oral 6-Month Regimen for Multidrug-Resistant Tuberculosis: A Multicenter, Randomized Controlled Clinical Trial (the NExT Study).

Am J Respir Crit Care Med. 2022 May 15;205(10):1214-1227. doi: 10.1164/rccm.202107-1779OC.

Esmail A(1)(2), Oelofse S(1)(2), Lombard C(3)(4), Perumal R(1)(2), Mbuthini L(1), Goolam Mahomed A(5), Variava E(6)(7)(8), Black J(9), Oluboyo P(10), Gwentshu N(11), Ngam E(11), Ackerman T(12), Marais L(12), Mottay L(1)(2), Meier S(1)(2), Pooran A(1)(2), Tomasicchio M(1)(2), Te Riele J(13), Derendinger B(14), Ndjeka N(15), Maartens G(16), Warren R(14), Martinson N(17)(18), Dheda K(1)(2)(19).

Comment in
Am J Respir Crit Care Med. 2022 May 15;205(10):1142-1144.

Rationale: Improving treatment outcomes while reducing drug toxicity and shortening the treatment duration to ∼6 months remains an aspirational goal for the treatment of multidrug-resistant/rifampicin-resistant tuberculosis (MDR/RR-TB). Objectives: To conduct a multicenter randomized controlled trial in adults with MDR/RR-TB (i.e., without resistance to fluoroquinolones or aminoglycosides). Methods: Participants were randomly assigned (1:1 ratio) to a ∼6-month all-oral regimen that included levofloxacin, bedaquiline, and linezolid, or the standard-of-care (SOC) ⩾9-month World Health Organization (WHO)-approved injectable-based regimen. The primary endpoint was a favorable WHO-defined treatment outcome (which mandates that prespecified drug substitution is counted as an unfavorable outcome) 24 months after treatment initiation. The trial was stopped prematurely when bedaquiline-based therapy became the standard of care in South Africa. Measurements and Main Results: In total, 93 of 111 randomized participants (44 in the comparator arm and 49 in the interventional arm) were included in the modified intention-to-treat analysis; 51 (55%) were HIV coinfected (median CD4 count, 158 cells/ml). Participants in the intervention arm were 2.2 times more likely to experience a favorable 24-month outcome than participants in the SOC arm (51% [25 of 49] vs. 22.7% [10 of 44]; risk ratio, 2.2 [1.2-4.1]; P = 0.006). Toxicity-related drug substitution occurred more frequently in the SOC arm (65.9% [29 of 44] vs. 34.7% [17 of 49]; P = 0.001)], 82.8% (24 of 29) owing to kanamycin (mainly hearing loss; replaced by bedaquiline) in the SOC arm, and 64.7% (11 of 17) owing to linezolid (mainly anemia) in the interventional arm. Adverse event-related treatment discontinuation in the safety population was more common in the SOC arm (56.4% [31 of 55] vs. 32.1% [17 of 56]; P = 0.007). However, grade 3 adverse events were more common in the interventional arm (55.4% [31 of 56] vs. 32.7 [18

of 55]; P = 0.022). Culture conversion was significantly better in the intervention arm (hazard ratio, 2.6 [1.4-4.9]; P = 0.003) after censoring those with bedaquiline replacement in the SOC arm (and this pattern remained consistent after censoring for drug replacement in both arms; P = 0.01). Conclusions: Compared with traditional injectable-containing regimens, an all-oral 6-month levofloxacin, bedaquiline, and linezolid-containing MDR/RR-TB regimen was associated with a significantly improved 24-month WHO-defined treatment outcome (predominantly owing to toxicity-related drug substitution). However, drug toxicity occurred frequently in both arms. These findings inform strategies to develop future regimens for MDR/RR-TB.Clinical trial registered with www.clinicaltrials.gov (NCT02454205).

DOI: 10.1164/rccm.202107-1779OC
PMID: 35175905 [Indexed for MEDLINE]

2. **Bedaquiline.**

Drugs and Lactation Database (LactMed) [Internet]. Bethesda (MD): National Library of Medicine (US); 2006–.
2022 May 15.

Data from two women taking bedaquiline and one of their breastfed infants indicate that exposure of the infant to the drug via breastmilk is substantial, with one infant having a therapeutic serum level. The clinical consequences of this exposure are unknown. The drug could protect the infant from multidrug-resistant tuberculosis, or could result in adverse effects. If bedaquiline is required by the mother, it is not a reason to discontinue breastfeeding. Monitor breastfed infants for adverse reactions, such as inadequate weight gain, liver toxicity, nausea, arthralgia, headache, hemoptysis, and chest pain.[1]

PMID: 31038856

3. **Characterisation of drug-resistant Mycobacterium tuberculosis mutations and transmission in Pakistan.**

Sci Rep. 2022 May 11;12(1):7703. doi: 10.1038/s41598-022-11795-4.

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

Tuberculosis, caused by Mycobacterium tuberculosis, is a high-burden disease in Pakistan, with multi-drug (MDR) and extensive-drug (XDR) resistance, complicating infection control. Whole genome sequencing (WGS) of M. tuberculosis is being used to infer lineages (strain-types), drug resistance mutations, and transmission patterns-all informing infection control and clinical decision making. Here we analyse WGS data on 535 M. tuberculosis isolates sourced across Pakistan between years 2003 and 2020, to understand the circulating strain-types and mutations related to 12 anti-TB drugs, as well as identify transmission clusters. Most isolates belonged to lineage 3 (n = 397; 74.2%) strain-types, and were MDR (n = 328; 61.3%) and (pre-)XDR (n = 113; 21.1%). By inferring close genomic relatedness between isolates (< 10-SNPs difference), there was evidence of M. tuberculosis transmission, with 55 clusters formed consisting of a total of 169 isolates. Three clusters consist of M. tuberculosis that are similar to isolates found outside of Pakistan. A genome-wide association analysis comparing 'transmitted' and 'non-transmitted' isolate groups, revealed the nusG gene as most significantly associated with a potential transmissible phenotype ($P = 5.8 \times 10\text{-}10$). Overall, our study provides important insights into M. tuberculosis genetic diversity and transmission in Pakistan, including providing information on circulating drug resistance mutations for monitoring activities and clinical decision making.

DOI: 10.1038/s41598-022-11795-4
PMCID: PMC9095715
PMID: 35545649 [Indexed for MEDLINE]

4. **The occurrence of multidrug-resistant Mycobacterium tuberculosis from patients of pulmonary tuberculosis.**

J Infect Dev Ctries. 2022 Apr 30;16(4):698-704. doi: 10.3855/jidc.14990.

Iqbal A(1), Shafique M(1), Zahoor MA(1), Muzammil S(1), Nawaz Z(1), Jabbar A(2), Khurshid M(1), Hussain R(3), Islam MA(4), Almatroudi A(5), Allemailem KS(5), Rasool MH(1), Aslam B(6).

INTRODUCTION: Multidrug-resistant Mycobacterium tuberculosis (MDR-TB) is one of the leading causes of death in the world. The resource constraints make it difficult to diagnose and monitor the cases of MDR-TB. GeneXpert is a recognized tool used to diagnose the patients of pulmonary tuberculosis in clinical settings across the globe.
METHODOLOGY: The present one-year cross-sectional study was conducted to estimate the occurrence of MDR-TB in patients with pulmonary TB. A total of 1000 patients suspected of pulmonary tuberculosis were included in this study. A

random convenient sampling technique was done to collect the sputum samples (twice) from the patients. Samples were processed for the detection of Mycobacterium tuberculosis using conventional detection methods like the Ziehl Nelson staining method and fluorescent microscopy. Additionally, Cepheid GeneXpert was used for molecular detection of MDR-TB in smear-positive samples of pulmonary tuberculosis by amplifying the rifampicin resistance determining region (RRDR; rpoB gene). All the tests were performed in the biosafety level III lab of District Headquarters Hospital Nankana Sahib.
RESULTS: It was observed that 103 (10.3%) individuals were diagnosed as positive for tuberculosis among 1000 patients. Among these 103 TB positive cases, there were 11 (10.7%) patients diagnosed with rifampicin resistance gene (RR-Gene) of Mycobacterium tuberculosis.
CONCLUSIONS: Overall findings of the study showed that MDR-TB is prevalent in pulmonary TB patients and GeneXpert is the most sensitive technique for early diagnosis of the disease, which may be very helpful in the treatment and control of this public health menace in low and middle-income countries.

DOI: 10.3855/jidc.14990
PMID: 35544633 [Indexed for MEDLINE]

5. Linezolid for patients with multidrug-resistant tuberculosis/extensively drug-resistant tuberculosis in China.

Drug Discov Ther. 2022 May 17;16(2):96-98. doi: 10.5582/ddt.2022.01024. Epub 2022 Apr 20.

Zhang P(1)(2), Tan J(1), Lin Y(1), Zhang H(1), Deng G(1), Chen X(2).

Linezolid has been one of the key anti-tuberculosis agents for the treatment of multidrug-resistant tuberculosis (MDR-TB)/extensively drug-resistant tuberculosis (XDR-TB). It used to be very expensive and was not covered by social insurance from local governments. Nevertheless, a growing number of patients in China received linezolid in their anti- MDR/XDR TB regimens over the past decade. Many scholars in China have reported their experience using linezolid to treat patients with MDR/XDR-TB. In view of this, existing evidence of the efficacy and safety of linezolid and problems faced by Chinese patients with MDR/XDR-TB are summarized here.

DOI: 10.5582/ddt.2022.01024

PMID: 35444071 [Indexed for MEDLINE]

6. Treatments of Multidrug-Resistant Tuberculosis: Light at the End of the Tunnel.

Am J Respir Crit Care Med. 2022 May 15;205(10):1142-1144. doi: 10.1164/rccm.202202-0393ED.

Lange C(1)(2)(3)(4), Barry CE 3rd(5), Horsburgh CR Jr(6)(7).

Comment on
Am J Respir Crit Care Med. 2022 May 15;205(10):1214-1227.
Am J Respir Crit Care Med. 2022 May 15;205(10):1228-1235.

DOI: 10.1164/rccm.202202-0393ED
PMID: 35320062 [Indexed for MEDLINE]

7. Drug-resistant tuberculosis: advances in diagnosis and management.

Curr Opin Pulm Med. 2022 May 1;28(3):211-217. doi: 10.1097/MCP.0000000000000866. Epub 2022 Feb 25.

Günther G(1)(2)(3), Ruswa N(4), Keller PM(5).

PURPOSE OF REVIEW: Diagnosis and treatment of drug-resistant tuberculosis (DR-TB) is undergoing substantial changes, owing availability of new diagnostic tools and drugs, coupled with global underdiagnosis and undertreatment. Recent developments are reviewed.
RECENT FINDINGS: Molecular diagnostics, for Mycobacterium tuberculosis complex detection and prediction of drug resistance, implemented in the last decade, accelerated TB diagnosis with improved case detection. Nevertheless, access and coverage of drug-resistance testing remain insufficient. Genome sequencing-technologies, based on targeted next-generation sequencing show early potential to mitigate some of the challenges in the future. The recommendation to use an all oral, bedaquiline based regimen for treatment of multidrug-resistant/rifampicin-resistant TB is major advancement in DR-TB care. TB regimen using new and repurposed TB drugs demonstrate in recent clinical trials like, NIX-TB, ZeNIX and TB PRACTECAL considerable treatment success, shorten treatment duration and reduce toxicity. Their optimal use is threatened by the rapid occurrence and spread of strains, resistant to new drugs. Children benefit only very slowly from the progress.
SUMMARY: There is notable progress in improved diagnosis and treatment of drug-resistant TB, but complicated by the COVID-19 pandemic the majority of TB patients worldwide don't have (yet) access to the advances.

DOI: 10.1097/MCP.0000000000000866
PMID: 35220372 [Indexed for MEDLINE]

8. Prospects of contezolid (MRX-I) against multidrug-resistant tuberculosis and extensively drug-resistant tuberculosis.

Drug Discov Ther. 2022 May 17;16(2):99-101. doi: 10.5582/ddt.2022.01025. Epub 2022 Apr 12.

Yang M(1), Zhan S(1), Fu L(1), Wang Y(1), Zhang P(1), Deng G(1).

Tuberculosis has become a great global public health threat. Compared with drug-susceptible tuberculosis (TB), the treatment regimens for multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) involve more severe adverse events and poorer treatment outcomes. Linezolid (LZD) is the first oxazolidinones used for TB. Thanks to its potent activity against Mycobacterium tuberculosis, LZD has become one of the key agents in the regimens against MDR/XDR-TB. However, this drug may cause intolerability and other adverse events. Contezolid, another novel oxazolidinone, can also inhibit M. tuberculosis, still with fewer adverse effects compared with LZD. This paper is to prospect the potentials of contezolid in the treatment of MDR/XDR-TB, with focus on its efficacy and possible adverse effects.

DOI: 10.5582/ddt.2022.01025
PMID: 35418550 [Indexed for MEDLINE]

9. Cost of TB prevention and treatment in the Philippines in 2017.

Int J Tuberc Lung Dis. 2022 May 1;26(5):392-398. doi: 10.5588/ijtld.21.0622.

Capeding TPJ(1), Rosa JD(1), Lam H(1), Gaviola DG(2), Garfin AMC(2), Hontiveros C(2), Cunnama L(3), Laurence YV(4), Kitson N(4), Vassall A(4), Sweeney S(4), Garcia-Baena I(5).

BACKGROUND: The Philippines aims to accelerate TB reduction through the provision of universally accessible and affordable services. The objectives of this paper are to estimate the costs of TB services and interventions using a health systems´ perspective, and to explore cost differences in service delivery via primary care facilities or hospitals.METHODS: Data were collected from a multi-stage stratified random sampling of 28 facilities in accordance with

Global Health Cost Consortium costing standards and analysis tools. Unit costs (in US$) estimated using top-down (TD) and bottom-up (BU) approaches, are summarised following Value TB reporting standards and by broad facility type.RESULTS: Cost of delivering 32 TB services and eight interventions varied by costing method and delivery platform. Average BU costs ranged from US$0.38 for treatment support visits, US$2.5 for BCG vaccination, US$19.48 for the Xpert® MTB/RIF test to US$3,677 for MDR-TB treatment using the long regimen. Delivering TB care in hospitals was generally more costly than in primary care facilities, except for TB prevention in children and MDR-TB treatment using the long regimen.CONCLUSION: Comprehensive costing data for TB care in the Philippines are now available to aid in the design, planning, and prioritisation of delivery models to End TB.

DOI: 10.5588/ijtld.21.0622
PMCID: PMC9067429
PMID: 35505478 [Indexed for MEDLINE]

10. **Proportion and trend of primary resistance among Multidrug resistant Tuberculosis patients in Ethiopia.**

J Clin Tuberc Other Mycobact Dis. 2022 Apr 25;27:100315. doi: 10.1016/j.jctube.2022.100315. eCollection 2022 May.

Bayissa A(1), Demissie M(2), Biru M(1), Akalu Z(1).

BACKGROUND: Evidence based information on the proportion & trend of primary resistance among multidrug resistance (MDR) TB patients is important for designing effective strategies in the control of the disease.
METHODS: A retrospective record review of 348 MDR/RR-TB patients treated at All African Leprosy Rehabilitation & Training (ALERT) Center from January 2014-December 2018. Categorical variables were compared using Chi-square/Fisher exact test as appropriate. Trend analysis was done using chi-square & linear regression. Logistic regression analysis was done to determine the factors associated with primary MDR/RR TB. Adjusted Odds Ratio (AOR) with 95% CI and p value < 5% were used to report factors associated.
RESULT: Proportion of primary resistance among MDR/RR TB patients was 25.9% with 95% CI 21.3-30.3%. The proportion increased form 9.7% in 2014 to 43.4% in 2018 at a yearly increasing rate of 9.27%. Contact history to TB patient & year of diagnosis 2017 and 2018 were significantly associated with primary resistance AOR (95% CI) & p value 4.15(1.75-9.84) p = 0.001, 3.87(1.44-10.39) p = 0.007, 3.43(1.20-9.84) p = 0.022 respectively.
CONCLUSION: The study revealed a high proportion of primary resistance among MDR/RR TB during the study period with a linearly increasing fashion thus a need for due attention in the efforts to control MDR TB.

DOI: 10.1016/j.jctube.2022.100315
PMCID: PMC9062340
PMID: 35521633

11. **Emerging threat of drug-resistant tuberculosis and trends in the era of COVID-19: A descriptive study from northwestern Nigeria.**

J Clin Tuberc Other Mycobact Dis. 2022 May 17;28:100319. doi: 10.1016/j.jctube.2022.100319. eCollection 2022 Aug.

Muhammad Dayyab F(1), Iliyasu G(2), Garba Ahmad B(3), Aliyu Umar I(4), Musa Shuaib N(5), Bajehson M(6), Muhammad Daiyab I(7), Akpala O(1), Remilekun O(1), Garba Habib A(2); For Kano TB Concilium Experts.

BACKGROUND: Mycobacterium tuberculosis with resistance to first line and second line anti tuberculous drugs is a serious setback in the treatment of tuberculosis (TB). The COVID-19 pandemic constitutes a serious threat that could unwind the recent gains made thus far in the control of tuberculosis. This study aims to explore the pattern of drug resistant tuberculosis (DRTB) in our institution. We also aimed to explore the changing trends of TB in the era of the COVID-19 pandemic.
METHODS: This descriptive study included all DRTB patients admitted and managed in the hospital between January 2018 and December 2020. We compare TB case detection in the facility before and after COVID-19 pandemic. Drug susceptibility testing were expressed as frequencies and percentages.
RESULTS: The study found that there was 66.03%, 45.09% and 77.78% drop in case detection of drug-sensitive TB (DSTB), DRTB and Fluoroquinolone (FQ) resistant TB respectively in the year 2020 compared to 2019. The drop in cases was similar when the year 2020 was compared to 2018. Among the 132 patients in the cohort, resistance to isoniazid, fluoroquinolones and second-line injectable agents were reported as 23.48%, 12.88%, and 31.06% respectively.
CONCLUSION: We question the potential reason why a drop in tuberculosis cases was observed in the year 2020 and we alert the Nigerian authorities that COVID-19 control efforts going hand-in-hand with intensified TB case finding and surveillance efforts and initiating proper TB treatment for persons with active TB are urgently needed.

DOI: 10.1016/j.jctube.2022.100319
PMCID: PMC9110314

PMID: 35599722

12. **Multidrug-resistant and extensively drug-resistant Mycobacterium tuberculosis strains in geriatrics: An analysis and its implications in tuberculosis control.**

J Clin Tuberc Other Mycobact Dis. 2022 Apr 30;27:100317. doi: 10.1016/j.jctube.2022.100317. eCollection 2022 May.

Verma AK(1), Yadav RN(1), Kumar G(1), Dewan RK(2).

OBJECTIVE: This study aimed to analyze the trends of tuberculosis (TB) disease, drugs susceptibility patterns in geriatric TB over a period of three years (from 2010 to 2012).
MATERIALS & METHODS: In this study, laboratory data on diagnosis of geriatric tuberculosis suspected patients (age ≥60 years) was analyzed retrospectively at National Reference Laboratory (NRL).
RESULTS: Among 12,140 geriatric TB suspects, 1621 (13%) were acid-fast bacillus (AFB) smear-positive and 10,519 (87%) were smear-negative. Analysis of 915 culture results showed 470 (51%) as positive for Mycobacterium tuberculosis complex (MTBC), 63 (7%) contaminated and 36 (4%) identified as mycobacteria other than tuberculosis (MOTT). A total 210/470 (45%) were multidrug-resistant TB (MDR-TB) strains. Among the mono-resistant strains, isoniazid mono-resistant was found more frequently (134/470, 28%) whereas, it was least among rifampicin mono-resistant 5/470 (1%). The second-line drug susceptibility testing (DST) results showed 7% (17/240) extensively drug-resistant TB (XDR-TB) strains. Most common second line mono-resistant strain was observed with ofloxacin, 16% (38/240).
CONCLUSION: This study shows high number of MDR/XDR geriatric TB patients at tertiary care TB hospital. The study highlighted the need of separate line of early identification, diagnosis and treatment of geriatric TB patients. However, further study with improved sample size may needed to confirm the findings.

DOI: 10.1016/j.jctube.2022.100317
PMCID: PMC9079229
PMID: 35541502

13. **Management of childhood MDR-TB in Europe and Central Asia: report of a Regional WHO meeting.**

Int J Tuberc Lung Dis. 2022 May 1;26(5):433-440. doi: 10.5588/ijtld.21.0541.

Gröschel MI(1), van den Boom M(2), Dixit A(3), Skrahina A(4), Dodd PJ(5),

Migliori GB(6), Seddon JA(7), Farhat MR(8).

BACKGROUND: As the WHO European Region has the highest proportion of multidrug-resistant TB (MDR-TB) among total incident TB cases, many children and adolescents are at risk of MDR-TB infection and disease.METHODS: We performed an electronic survey of clinicians and TB programme personnel who attended the 2020 Regional Consultation on child and adolescent TB organised by the WHO Regional Office. We characterised access to diagnostics and drugs, and practices in the prevention and management of child and adolescent MDR-TB.RESULTS: Children and adolescents are inconsistently represented in national guidelines and budgets; child-friendly drug formulations for MDR-TB treatment are insufficiently available in 57% of countries, and 32% of countries reported paediatric drug stock-outs. The novel drugs, bedaquiline and delamanid, are accessible by respectively 80% and 60% of respondent countries. Respondents were asked how many children were diagnosed with MDR-TB in 2019, and a comparison of this number to modelled estimates of incidence (to identify the case detection gap) and WHO notifications (to identify the case reporting gap) showed substantial differences in both comparisons.CONCLUSIONS: Better representation of this patient group in guidelines and budgets, greater access to drugs and improved reporting are essential to reach TB elimination in this Region.

DOI: 10.5588/ijtld.21.0541
PMID: 35505487 [Indexed for MEDLINE]

14. **Evolution and spread of a highly drug resistant strain of Mycobacterium tuberculosis in Papua New Guinea.**

BMC Infect Dis. 2022 May 6;22(1):437. doi: 10.1186/s12879-022-07414-2.

Bainomugisa A(#)(1), Lavu E(#)(2)(3), Pandey S(1), Majumdar S(4)(5), Banamu J(3), Coulter C(1), Marais B(6), Coin L(7), Graham SM(4)(5), du Cros P(8).

BACKGROUND: Molecular mechanisms determining the transmission and prevalence of drug resistant tuberculosis (DR-TB) in Papua New Guinea (PNG) are poorly understood. We used genomic and drug susceptibility data to explore the evolutionary history, temporal acquisition of resistance and transmission dynamics of DR-TB across PNG.
METHODS: We performed whole genome sequencing on isolates from Central Public Health Laboratory, PNG, collected 2017-2019. Data analysis was done on a composite dataset that also included 100 genomes previously sequenced from Daru, PNG (2012-2015).
RESULTS: Sampled isolates represented 14 of the 22 PNG provinces, the majority (66/94; 70%) came from the National Capital District (NCD). In the composite dataset, 91% of strains were Beijing 2.2.1.1, identified in 13 provinces.

Phylogenetic tree of Beijing strains revealed two clades, Daru dominant clade (A) and NCD dominant clade (B). Multi-drug resistance (MDR) was repeatedly and independently acquired, with the first MDR cases in both clades noted to have emerged in the early 1990s, while fluoroquinolone resistance emerged in 2009 (95% highest posterior density 2000-2016). We identified the presence of a frameshift mutation within Rv0678 (p.Asp47fs) which has been suggested to confer resistance to bedaquiline, despite no known exposure to the drug. Overall genomic clustering was significantly associated with rpoC compensatory and inhA promoter mutations ($p < 0.001$), with high percentage of most genomic clusters (12/14) identified in NCD, reflecting its role as a potential national amplifier.
CONCLUSIONS: The acquisition and evolution of drug resistance among the major clades of Beijing strain threaten the success of DR-TB treatment in PNG. With continued transmission of this strain in PNG, genotypic drug resistance surveillance using whole genome sequencing is essential for improved public health response to outbreaks. With occurrence of resistance to newer drugs such as bedaquiline, knowledge of full drug resistance profiles will be important for optimal treatment selection.

DOI: 10.1186/s12879-022-07414-2
PMCID: PMC9077924
PMID: 35524232 [Indexed for MEDLINE]

15. **Chest X-ray findings in drug-sensitive and drug-resistant pulmonary tuberculosis patients in Uganda.**

J Clin Tuberc Other Mycobact Dis. 2022 Mar 25;27:100312. doi: 10.1016/j.jctube.2022.100312. eCollection 2022 May.

Oriekot A(1), Sereke SG(1), Bongomin F(2), Bugeza S(1), Muyinda Z(3).

BACKGROUND: Tuberculosis (TB) is one of the leading causes of death worldwide. Radiology has an important role in the diagnosis of both drug-sensitive (DS) and rifampicin-resistant (RR) pulmonary TB (PTB). This study aimed to compare the chest x-ray (CXR) patterns of microbiologically confirmed DS and RR PTB cases stratified by HIV serostatus in Uganda.
METHODS: We conducted a hospital-based retrospective study at the Mulago National Referral Hospital (MNRH) TB wards. All participants had a microbiologically confirmed diagnosis of PTB. CXR findings extracted included infiltrates, consolidation, cavity, fibrosis, bronchiectasis, atelectasis, and other non-lung parenchymal findings. All films were examined by two independent radiologists blinded to the clinical diagnosis.

RESULTS: We analyzed CXR findings of 165 participants: 139 DS- and 26 RR-TB cases. The majority (n = 118, 71.7%) of the participants were seronegative for HIV. Overall, 5/165 (3%) participants had normal CXR. There was no statistically significant difference in the proportion of participants with consolidations (74.8% versus 88.5%; p = 0.203), bronchopneumonic opacities (56.1% versus 42.3%, p = 0.207) and cavities (38.1% versus 46.2%, p = 0.514), across drug susceptibility status (DS versus RR TB). Among HIV-infected participants, consolidations were predominantly in the middle lung zone in the DS TB group and in the lower lung zone in the RR TB group (42.5% versus 12.8%, p = 0.66). HIV-infected participants with RR TB had statistically significantly larger cavity sizes compared to their HIV uninfected counterparts with RR TB (7.7 ± 6.8 cm versus 4.2 ± 1.3 cm, p = 0.004).
CONCLUSIONS: We observed that a vast majority of participants had similar CXR changes, irrespective of drug susceptibility status. However, HIV-infected RR PTB had larger cavities.The diagnostic utility of cavity sizes for the differentiation of HIV-infected and non-infected RR TB could be investigated further.

DOI: 10.1016/j.jctube.2022.100312
PMCID: PMC8958542
PMID: 35355939

16. **Characteristics and Trend of Drug-Resistant Tuberculosis at a Major Specialized Hospital in Chongqing, China: 2016 Versus 2019.**

Disaster Med Public Health Prep. 2022 May 16:1-7. doi: 10.1017/dmp.2022.88. Online ahead of print.

Zhang H(1), Zhang K(2)(3), Yang X(4), Luo M(1), Li C(5), Wang X(6), Hu K(7).

OBJECTIVE: The epidemic of drug-resistant tuberculosis (DR-TB) has become a major concern in global TB control. This study aimed to investigate the patterns and trend of DR-TB epidemic between different time periods in Chongqing.
METHODS: A total of 985 and 835 culture positive TB patients with drug susceptibility testing (DST) results admitted to the hospital in 2016 and 2019, respectively, were included. Chi-square testing was used to compare the prevalence and trends of DR-TB in 2016 and 2019.
RESULTS: The proportion of previously treated TB cases with culture positivity was 45.7% in 2019, significantly higher than that in 2016 (39.1%, P = 0.004). The overall rate of drug resistance in 2019 was 43.1%, higher than that in 2016 (40.2%). The rates of multi-drug resistant TB (MDR-TB) and pre-extensively drug resistant TB (pre-XDR-TB) increased significantly from 2016 to 2019 among all TB

cases (MDR: 25% vs 33.4%, P < 0.001 and pre-XDR: 7.1% vs 12.8%, P < 0.001, respectively) and previously treated TB cases (MDR: 46.5% vs 56%, P = 0.008 and pre-XDR: 13.2% vs 21.5%, P = 0.003, respectively).
CONCLUSIONS: Our findings indicated that the prevalence of DR-TB remains high in Chongqing. The trend of resistance to anti-TB drugs beccame worse between 2016 and 2019. Moreover, acquired MDR may play a major role in MDR-TB epidemic in Chongqing. Therefore, rapid diagnosis and effective treatment of TB patients will be important to reduce the burden of DR-TB in Chongqing.

DOI: 10.1017/dmp.2022.88
PMID: 35575296

17. Rise of drug-resistant tuberculosis is hidden in plain sight.

Nature. 2022 May;605(7910):417-418. doi: 10.1038/d41586-022-01342-6.

Ledford H.

DOI: 10.1038/d41586-022-01342-6
PMID: 35578020 [Indexed for MEDLINE]

18. Whole genome sequencing-based drug resistance predictions of multidrug-resistant Mycobacterium tuberculosis isolates from Tanzania.

JAC Antimicrob Resist. 2022 Apr 21;4(2):dlac042. doi: 10.1093/jacamr/dlac042. eCollection 2022 Apr.

Mbelele PM(1)(2), Utpatel C(3)(4), Sauli E(2), Mpolya EA(2), Mutayoba BK(5)(6), Barilar I(3)(4), Dreyer V(3)(4), Merker M(3)(7), Sariko ML(8), Swema BM(8), Mmbaga BT(8)(9), Gratz J(10), Addo KK(11), Pletschette M(6)(12), Niemann S(3)(4), Houpt ER(10), Mpagama SG(1)(2)(8)(9), Heysell SK(10).

BACKGROUND: Rifampicin- or multidrug-resistant (RR/MDR) Mycobacterium tuberculosis complex (MTBC) strains account for considerable morbidity and mortality globally. WGS-based prediction of drug resistance may guide clinical decisions, especially for the design of RR/MDR-TB therapies.
METHODS: We compared WGS-based drug resistance-predictive mutations for 42 MTBC isolates from MDR-TB patients in Tanzania with the MICs of 14 antibiotics measured in the Sensititre™ MycoTB assay. An isolate was phenotypically categorized as resistant if it had an MIC above the epidemiological-cut-off (ECOFF) value, or as susceptible if it had an MIC below or equal to the ECOFF.
RESULTS: Overall, genotypically non-wild-type MTBC isolates with high-level resistance mutations (gNWT-R) correlated with isolates with MIC values above the ECOFF. For instance, the median MIC value (mg/L) for rifampicin-gNWT-R strains

was >4.0 (IQR 4.0-4.0) compared with 0.5 (IQR 0.38-0.50) in genotypically wild-type (gWT-S, P < 0.001); isoniazid-gNWT-R >4.0 (IQR 2.0-4.0) compared with 0.25 (IQR 0.12-1.00) among gWT-S (P = 0.001); ethionamide-gNWT-R 15.0 (IQR 10.0-20.0) compared with 2.50 (IQR; 2.50-5.00) among gWT-S (P < 0.001). WGS correctly predicted resistance in 95% (36/38) and 100% (38/38) of the rifampicin-resistant isolates with ECOFFs >0.5 and >0.125 mg/L, respectively. No known resistance-conferring mutations were present in genes associated with resistance to fluoroquinolones, aminoglycosides, capreomycin, bedaquiline, delamanid, linezolid, clofazimine, cycloserine, or p-amino salicylic acid. CONCLUSIONS: WGS-based drug resistance prediction worked well to rule-in phenotypic drug resistance and the absence of second-line drug resistance-mediating mutations has the potential to guide the design of RR/MDR-TB regimens in the future.

DOI: 10.1093/jacamr/dlac042
PMCID: PMC9021016
PMID: 35465240

19. CinA mediates multidrug tolerance in Mycobacterium tuberculosis.

Nat Commun. 2022 Apr 22;13(1):2203. doi: 10.1038/s41467-022-29832-1.

Kreutzfeldt KM(1), Jansen RS(2)(3), Hartman TE(2), Gouzy A(1), Wang R(1)(4), Krieger IV(5), Zimmerman MD(6), Gengenbacher M(6), Sarathy JP(6), Xie M(6), Dartois V(6), Sacchettini JC(5), Rhee KY(2)(1), Schnappinger D(7), Ehrt S(8).

The ability of Mycobacterium tuberculosis (Mtb) to resist and tolerate antibiotics complicates the development of improved tuberculosis (TB) chemotherapies. Here we define the Mtb protein CinA as a major determinant of drug tolerance and as a potential target to shorten TB chemotherapy. By reducing the fraction of drug-tolerant persisters, genetic inactivation of cinA accelerated killing of Mtb by four antibiotics in clinical use: isoniazid, ethionamide, delamanid and pretomanid. Mtb ΔcinA was killed rapidly in conditions known to impede the efficacy of isoniazid, such as during nutrient starvation, during persistence in a caseum mimetic, in activated macrophages and during chronic mouse infection. Deletion of CinA also increased in vivo killing of Mtb by BPaL, a combination of pretomanid, bedaquiline and linezolid that is used to treat highly drug-resistant TB. Genetic and drug metabolism studies suggest that CinA mediates drug tolerance via cleavage of NAD-drug adducts.

DOI: 10.1038/s41467-022-29832-1
PMCID: PMC9033802
PMID: 35459278 [Indexed for MEDLINE]

20. **Challenges in the screening and treatment of latent multidrug-resistant tuberculosis infection.**

Drug Discov Ther. 2022 May 17;16(2):52-54. doi: 10.5582/ddt.2022.01029. Epub 2022 Apr 23.

Deng G(1), Zhang P(1), Lu H(1).

Individuals in close contact with multidrug-resistant tuberculosis (MDR-TB) patients are subject to an elevated risk of infection, and may develop latent MDR-TB infection. Numerous studies have described latent tuberculosis infection (LTBI) as a reservoir of new TB disease. The screening and treatment of latent MDR-TB infection are challenging. Hereby, we reviewed the epidemiology, current management and prevention approach of LTBI in MDR-TB close contacts, to provide additional information for future research direction and policy design formulation to reduce the LTBI reservoir.

DOI: 10.5582/ddt.2022.01029
PMID: 35466125 [Indexed for MEDLINE]

21. **Molecular characteristics of Mycobacterium tuberculosis drug-resistant isolates from HIV- and HIV+ tuberculosis patients in Russia.**

BMC Microbiol. 2022 May 19;22(1):138. doi: 10.1186/s12866-022-02553-7.

Panova AE(1), Vinokurov AS(1), Shemetova AA(1), Burmistrova IA(1), Shulgina MV(2), Samoilova AG(1), Vasilyeva IA(1), Vakhrusheva DV(3), Umpeleva TV(3), Eremeeva NI(3), Lavrenchuk LS(3), Golubeva LA(3), Danilova TI(4), Vasilyeva TB(4), Ugol'kova VA(4), Sosova NV(5), Lekhlyaider MV(6), Gorshkova IA(6), Romanova TA(7).

BACKGROUND: High burden of drug-resistant (DR) tuberculosis (TB) is a significant threat to national TB control programs all over the world and in the Russian Federation. Different Mycobacterium tuberculosis (MTB) genotypes are hypothesized to have specific characteristics affecting TB control programs. For example, Beijing strains are supposed to have higher mutation rates compared to strains of other genotypes and subsequently higher capability to develop drug-resistance.
RESULTS: Clinical MTB isolates from HIV- and HIV+ patients from four regions of

Russia were analyzed for genotypes and mutations conferring resistance to Isoniazid, Rifampicin, Ethambutol, aminoglycosides, and fluoroquinolones. Analysis of genotypes and polymorphism of genomic loci according to the HIV status of the patients - sources of MTB isolates were performed. Studied MTB isolates from HIV- TB patients belonged to 15 genotypes and from HIV + TB patients - to 6 genotypes. Beijing clinical isolates dominated in HIV- (64,7%) and HIV+ (74,4%) groups. Other isolates were of LAM (including LAM1 and LAM9), Ural, and 4 minor groups of genotypes (including 5 subclones T). The spectrum of genotypes in the HIV- group was broader than in the HIV+ group. PR of B0/W148 Beijing was significantly lower than of other Beijing genotypes in susceptible and MDR-XDR isolates. Rates of isolates belonging to non-Beijing genotypes were higher than Beijing in susceptible isolates from HIV- patients.
CONCLUSIONS: Beijing genotype isolates prevailed in clinical isolates of all drug susceptibility profiles both from HIV- and HIV+ patients, although B0/W148 Beijing genotype did not dominate in this study. Genome loci and mutations polymorphisms were more pronounced in clinical isolates from HIV- patients, than from HIV+.

DOI: 10.1186/s12866-022-02553-7
PMCID: PMC9118847
PMID: 35590243 [Indexed for MEDLINE]

22. **In vitro anti-tuberculosis effect of probiotic Lacticaseibacillus rhamnosus PMC203 isolated from vaginal microbiota.**

Sci Rep. 2022 May 18;12(1):8290. doi: 10.1038/s41598-022-12413-z.

Rahim MA(#)(1)(2), Seo H(#)(1), Kim S(1), Tajdozian H(1)(2), Barman I(1)(2), Lee Y(1)(2), Lee S(1), Song HY(3)(4).

Mycobacterium tuberculosis (M. tb), the etiological agent of tuberculosis (TB), poses a severe challenge for public health and remains the number one cause of death as a single infectious agent. There are 10 million active cases of TB per year with 1.5 million deaths, and 2-3 billion people are estimated to harbor latent M. tb infection. Moreover, the emergence of multi-drug-resistant (MDR), extremely-drug-resistant (XDR), and the recent totally drug-resistant (TDR) M. tb is becoming a global issue that has fueled the need to find new drugs different from existing regimens. In these circumstances, probiotics can be a potential choice, so we focused on developing them as an anti-tuberculosis drug candidate. Here, we report the anti-tubercular activities of Lacticaseibacillus rhamnosus PMC203 isolated from the vaginal microbiota of healthy women. PMC203 exhibited a promising intracellular killing effect against both drug-sensitive

and resistant M. tb infected murine macrophage cell line RAW 264.7 without showing any cytotoxicity. Additionally, it also inhibited the growth of M. tb under broth culture medium. PMC203 did not cause weight change or specific clinical symptoms in a 2-week repeated oral administration toxicity test in a guinea pig model. Here, we also found that PMC203 induces autophagy in a dose dependent manner by increasing the signal of well-known autophagy gene markers, suggesting a possible intracellular killing mechanism.

DOI: 10.1038/s41598-022-12413-z
PMCID: PMC9116076
PMID: 35585245 [Indexed for MEDLINE]

23. Whole genome sequencing of multidrug-resistant Mycobacterium tuberculosis isolates collected in the Czech Republic, 2005-2020.

Sci Rep. 2022 May 3;12(1):7149. doi: 10.1038/s41598-022-11287-5.

Dohál M(1), Dvořáková V(2), Šperková M(2), Pinková M(2), Spitaleri A(3), Norman A(4), Cabibbe AM(3), Rasmussen EM(4), Porvazník I(5)(6), Škereňová M(7)(8), Solovič I(5)(6), Cirillo DM(3), Mokrý J(9).

The emergence and spread of resistant tuberculosis (TB) pose a threat to public health, so it is necessary to diagnose the drug-resistant forms in a clinically short time frame and closely monitor their transmission. In this study, we carried out a first whole genome sequencing (WGS)-based analysis of multidrug resistant (MDR) M. tuberculosis strains to explore the phylogenetic lineages diversity, drug resistance mechanisms, and ongoing transmission chains within the country. In total, 65 isolates phenotypically resistant to at least rifampicin and isoniazid collected in the Czech Republic in 2005-2020 were enrolled for further analysis. The agreement of the results obtained by WGS with phenotypic drug susceptibility testing (pDST) in the determination of resistance to isoniazid, rifampicin, pyrazinamide, streptomycin, second-line injectables and fluoroquinolones was more than 80%. Phylogenetic analysis of WGS data revealed that the majority of MDR M. tuberculosis isolates were the Beijing lineage 2.2.1 (n = 46/65; 70.8%), while the remaining strains belonged to Euro-American lineage. Cluster analysis with a predefined cut-off distance of less than 12 single nucleotide polymorphisms between isolates showed 19 isolates in 6 clusters (clustering rate 29.2%), located mainly in the region of the capital city of Prague. This study highlights the utility of WGS as a high-resolution approach in the diagnosis, characterization of resistance patterns, and molecular-epidemiological analysis of resistant TB in the country.

DOI: 10.1038/s41598-022-11287-5
PMCID: PMC9062869
PMID: 35505072 [Indexed for MEDLINE]

24. Performance of the GenoType MTBDRsl in a programmatic setting, South Africa.

Int J Tuberc Lung Dis. 2022 May 1;26(5):426-432. doi: 10.5588/ijtld.21.0590.

Lutchminarain K(1), Kajee A(1), Gandhi NR(2), Han KSS(1), Mvelase N(1).

Comment in
Int J Tuberc Lung Dis. 2022 May 1;26(5):385-387.

BACKGROUND: The GenoType MTBDRsl v2 is a molecular test designed for the rapid detection of resistance to second-line anti-TB drugs in Mycobacterium tuberculosis complex (MTBC).OBJECTIVE: To assess the use of MTBDRsl in a programmatic setting and to describe the resistance patterns in a high HIV-TB-endemic area in South Africa.METHODS: We performed a retrospective data analysis of all MTBDRsl results in patients with newly diagnosed rifampicin-resistant TB (RR-TB). We compared its performance on direct testing of smear-positive and smear-negative specimens. Results were examined to observe the detected resistance-conferring mutations.RESULTS: Of 1873 RR-TB/multidrug-resistant TB (MDR-TB), 37.4% were smear-negative and 62.5% were smear-positive. Among smear-negative specimens, the MTBDRsl showed an inconclusive rate of 61.2%, while the inconclusive rate from smear-positive specimens was 6.6%. The most common mutation observed in case of fluoroquinolone resistance occurred at the gyrA gene, codon 90 (A90V) (61/158, 38.6%), and the most common mutation in injectable aminoglycoside resistance occurred in the rrs region, A1401G (71/108, 65.7%).CONCLUSION: In HIV-TB-prevalent settings, routine use of the MTBDRsl is more effective when performed directly on smear-positive specimens. In view of currently used injectable-free regimens, this test requires revision.

DOI: 10.5588/ijtld.21.0590
PMID: 35505490 [Indexed for MEDLINE]

25. Leveraging Experience From Active TB Drug-Safety Monitoring and Management for Monitoring Active Antiretroviral Toxicity.

Glob Health Sci Pract. 2022 Apr 29;10(2):e2100595. doi: 10.9745/GHSP-D-21-00595.
Print 2022 Apr 28.

Stevens L(1), Perry KE(2), Moide I(3), Kaemala F(3), Nankinga J(3), Innes AL(4), Mogaba I(3).

Systems established for active drug safety monitoring and management of drug-resistant TB should be leveraged to ensure comprehensive surveillance for active toxicity monitoring during scale-up of newer antiretroviral regimens.

The introduction of novel medicines and regimens for antiretroviral (ARV) and TB treatment requires comprehensive surveillance systems for adverse events and adverse drug reactions. Many TB programs have introduced and institutionalized active drug safety monitoring and management (aDSM) platforms for drug-resistant TB. Because HIV programs must develop active ARV toxicity monitoring systems to ensure safe global scale-up of newer regimens, such as tenofovir-lamivudine-dolutegravir, we propose building on existing aDSM infrastructure to actively monitor ARV regimens as a synergistic TB/HIV collaborative activity and to narrow active toxicity monitoring gaps.

DOI: 10.9745/GHSP-D-21-00595
PMCID: PMC9053160
PMID: 35487562 [Indexed for MEDLINE]

26. **Comparison of efficacy of bedaquiline and moxifloxacin in drug resistant pulmonary tuberculosis. A prospective observational study.**

Monaldi Arch Chest Dis. 2022 May 4. doi: 10.4081/monaldi.2022.2231. Online ahead of print.

Desai G(1), Purohit G(2), Borana H(3), Deokar K(4), Yogi S(5).

Drug-resistant tuberculosis remains a major public health concern in many countries. We compared the efficacy and safety of bedaquiline plus optimized background regimen (Bdq+OBR) with high dose moxifloxacin and optimized background regimen (Mfx(h)+OBR) for the treatment of patients with multidrug-resistant tuberculosis with additional resistance to fluoroquinolones. In this prospective observational study, newly diagnosed cases of multidrug-resistant tuberculosis with additional resistance to fluoroquinolone were enrolled. They received either Bdq+OBR or Mfx(h)+OBR and were followed up for six months. The sputum culture conversion rate at the end of six months and the time to culture conversion in each group were studied. The safety profile of both regimens was also studied. The sputum culture conversion was achieved in 41 patients (100%) in the Bdq+OBR group and 36 patients (87.8%) in the Mfx(h)+OBR group at the end of 6 months. The mean time to culture conversion was found to be 3.10±0.8 months in the Bdq+OBR group and 3.32±0.9 months in the Mfx(h)+OBR group. Mortality was 6.8% in the Bdq+OBR group and 10.8 % in the Mfx(h)+OBR

group at 6 months. Raised serum lipase and dark discolouration of skin were significantly more common in the Bdq+OBR group while vomiting and ototoxicity were more common in the Mfx(h)+OBR group. Bdq+OBR was associated with higher success of sputum culture conversion at 6 months and faster sputum culture conversion rate as compared to the Mfx(h)+OBR.

DOI: 10.4081/monaldi.2022.2231
PMID: 35535455

27. **Xpert MTB/XDR for detection of pulmonary tuberculosis and resistance to isoniazid, fluoroquinolones, ethionamide, and amikacin.**

Cochrane Database Syst Rev. 2022 May 18;5(5):CD014841. doi: 10.1002/14651858.CD014841.pub2.

Pillay S(1), Steingart KR(2), Davies GR(3), Chaplin M(4), De Vos M(5), Schumacher SG(5), Warren R(1), Theron G(1).

Update of
doi: 10.1002/14651858.CD014841.

BACKGROUND: The World Health Organization (WHO) End TB Strategy stresses universal access to drug susceptibility testing (DST). DST determines whether Mycobacterium tuberculosis bacteria are susceptible or resistant to drugs. Xpert MTB/XDR is a rapid nucleic acid amplification test for detection of tuberculosis and drug resistance in one test suitable for use in peripheral and intermediate level laboratories. In specimens where tuberculosis is detected by Xpert MTB/XDR, Xpert MTB/XDR can also detect resistance to isoniazid, fluoroquinolones, ethionamide, and amikacin.
OBJECTIVES: To assess the diagnostic accuracy of Xpert MTB/XDR for pulmonary tuberculosis in people with presumptive pulmonary tuberculosis (having signs and symptoms suggestive of tuberculosis, including cough, fever, weight loss, night sweats). To assess the diagnostic accuracy of Xpert MTB/XDR for resistance to isoniazid, fluoroquinolones, ethionamide, and amikacin in people with tuberculosis detected by Xpert MTB/XDR, irrespective of rifampicin resistance (whether or not rifampicin resistance status was known) and with known rifampicin resistance.
SEARCH METHODS: We searched multiple databases to 23 September 2021. We limited searches to 2015 onwards as Xpert MTB/XDR was launched in 2020.
SELECTION CRITERIA: Diagnostic accuracy studies using sputum in adults with presumptive or confirmed pulmonary tuberculosis. Reference standards were culture (pulmonary tuberculosis detection); phenotypic DST (pDST), genotypic DST (gDST),composite (pDST and gDST) (drug resistance detection).
DATA COLLECTION AND ANALYSIS: Two review authors independently reviewed reports

for eligibility and extracted data using a standardized form. For multicentre studies, we anticipated variability in the type and frequency of mutations associated with resistance to a given drug at the different centres and considered each centre as an independent study cohort for quality assessment and analysis. We assessed methodological quality with QUADAS-2, judging risk of bias separately for each target condition and reference standard. For pulmonary tuberculosis detection, owing to heterogeneity in participant characteristics and observed specificity estimates, we reported a range of sensitivity and specificity estimates and did not perform a meta-analysis. For drug resistance detection, we performed meta-analyses by reference standard using bivariate random-effects models. Using GRADE, we assessed certainty of evidence of Xpert MTB/XDR accuracy for detection of resistance to isoniazid and fluoroquinolones in people irrespective of rifampicin resistance and to ethionamide and amikacin in people with known rifampicin resistance, reflecting real-world situations. We used pDST, except for ethionamide resistance where we considered gDST a better reference standard.

MAIN RESULTS: We included two multicentre studies from high multidrug-resistant/rifampicin-resistant tuberculosis burden countries, reporting on six independent study cohorts, involving 1228 participants for pulmonary tuberculosis detection and 1141 participants for drug resistance detection. The proportion of participants with rifampicin resistance in the two studies was 47.9% and 80.9%. For tuberculosis detection, we judged high risk of bias for patient selection owing to selective recruitment. For ethionamide resistance detection, we judged high risk of bias for the reference standard, both pDST and gDST, though we considered gDST a better reference standard. Pulmonary tuberculosis detection - Xpert MTB/XDR sensitivity range, 98.3% (96.1 to 99.5) to 98.9% (96.2 to 99.9) and specificity range, 22.5% (14.3 to 32.6) to 100.0% (86.3 to 100.0); median prevalence of pulmonary tuberculosis 91.3%, (interquartile range, 89.3% to 91.8%), (2 studies; 1 study reported on 2 cohorts, 1228 participants; very low-certainty evidence, sensitivity and specificity). Drug resistance detection People irrespective of rifampicin resistance - Isoniazid resistance: Xpert MTB/XDR summary sensitivity and specificity (95% confidence interval (CI)) were 94.2% (87.5 to 97.4) and 98.5% (92.6 to 99.7) against pDST, (6 cohorts, 1083 participants, moderate-certainty evidence, sensitivity and specificity). - Fluoroquinolone resistance: Xpert MTB/XDR summary sensitivity and specificity were 93.2% (88.1 to 96.2) and 98.0% (90.8 to 99.6) against pDST, (6 cohorts, 1021 participants; high-certainty evidence, sensitivity; moderate-certainty evidence, specificity). People with known rifampicin resistance - Ethionamide resistance: Xpert MTB/XDR summary sensitivity and specificity were 98.0% (74.2 to 99.9) and 99.7% (83.5 to 100.0) against gDST, (4 cohorts, 434 participants; very low-certainty evidence, sensitivity and specificity). - Amikacin resistance: Xpert MTB/XDR summary sensitivity and specificity were 86.1% (75.0 to 92.7) and 98.9% (93.0 to 99.8) against pDST, (4 cohorts, 490 participants; low-certainty evidence, sensitivity;

high-certainty evidence, specificity). Of 1000 people with pulmonary tuberculosis, detected as tuberculosis by Xpert MTB/XDR: - where 50 have isoniazid resistance, 61 would have an Xpert MTB/XDR result indicating isoniazid resistance: of these, 14/61 (23%) would not have isoniazid resistance (FP); 939 (of 1000 people) would have a result indicating the absence of isoniazid resistance: of these, 3/939 (0%) would have isoniazid resistance (FN). - where 50 have fluoroquinolone resistance, 66 would have an Xpert MTB/XDR result indicating fluoroquinolone resistance: of these, 19/66 (29%) would not have fluoroquinolone resistance (FP); 934 would have a result indicating the absence of fluoroquinolone resistance: of these, 3/934 (0%) would have fluoroquinolone resistance (FN). - where 300 have ethionamide resistance, 296 would have an Xpert MTB/XDR result indicating ethionamide resistance: of these, 2/296 (1%) would not have ethionamide resistance (FP); 704 would have a result indicating the absence of ethionamide resistance: of these, 6/704 (1%) would have ethionamide resistance (FN). - where 135 have amikacin resistance, 126 would have an Xpert MTB/XDR result indicating amikacin resistance: of these, 10/126 (8%) would not have amikacin resistance (FP); 874 would have a result indicating the absence of amikacin resistance: of these, 19/874 (2%) would have amikacin resistance (FN).

AUTHORS' CONCLUSIONS: Review findings suggest that, in people determined by Xpert MTB/XDR to be tuberculosis-positive, Xpert MTB/XDR provides accurate results for detection of isoniazid and fluoroquinolone resistance and can assist with selection of an optimised treatment regimen. Given that Xpert MTB/XDR targets a limited number of resistance variants in specific genes, the test may perform differently in different settings. Findings in this review should be interpreted with caution. Sensitivity for detection of ethionamide resistance was based only on Xpert MTB/XDR detection of mutations in the inhA promoter region, a known limitation. High risk of bias limits our confidence in Xpert MTB/XDR accuracy for pulmonary tuberculosis. Xpert MTB/XDR's impact will depend on its ability to detect tuberculosis (required for DST), prevalence of resistance to a given drug, health care infrastructure, and access to other tests.

DOI: 10.1002/14651858.CD014841.pub2
PMCID: PMC9115865
PMID: 35583175 [Indexed for MEDLINE]

28. Trends in rifampicin and isoniazid resistance in patients with presumptive TB.

Int J Tuberc Lung Dis. 2022 May 1;26(5):446-453. doi: 10.5588/ijtld.21.0455.

Palani N(1), Premkumar M(1), Vaishnavee V(1), Dinesh V(1), Thiruvengadam K(1), Lavanya J(2), Sridhar R(3), Frederick A(4), Sivaramakrishnan G(1), Mondal R(5), Padmapriyadarsini C(1), Shanmugam S(1).

BACKGROUND: Early diagnosis of drug-resistant TB (DR-TB) is crucial in preventing the spread of the disease in the community. Introduction of upfront decentralised drug susceptibility testing to district-level as part of universal drug susceptibility testing (UDST) policy increased the feasibility of rapid and early testing for drug resistance closer to the patient and has resulted in reduced circumstances for transmission. The introduction of the first-line line-probe assay (FL-LPA), GenoType® MTBDRplus v2, has had an extensive impact on the management of multidrug-resistant TB (MDR-TB) in India.MATERIALS and METHODS: Sputum samples of patients with presumptive TB and DR-TB from selected districts of Tamil Nadu received through National TB Elimination Programme (NTEP) were subjected to FL-LPA as per programme guidelines. In this study, we present trends in genotypic resistance to isoniazid (INH) and rifampicin (RIF) during the 4 years (2016-2019) among these patients. Band patterns were analysed as per the updated GLI (Global Laboratory Initiative) LPA interpretation and reporting guidelines.RESULTS: A total of 26,349 samples were received during the study period. Smear-positive samples (n = 20231) were directly subjected to FL-LPA; smear-negative samples were cultured in liquid media and M. tuberculosis-positive cultures were tested using FL-LPA. A total of 18,441 were MTB-positive on FL-LPA. INH monoresistance, RIF monoresistance and MDR-TB was observed in respectively 8.7%, 1.1% and 3.3% of the samples. There was a decreasing trend in all types of resistance observed particularly after 2017 ($P < 0.001$). MDR-TB showed a steady decrease from 5.6% to 1.8%. S531L (19.5%) and S315T (61.1%) were the most common mutations identified in the rpoB and katG genes, respectively. The percentage of inhA-c-15t promoter mutation, indicating low-level INH resistance, showed a consistent increase ($P < 0.001$).CONCLUSION: The impact of the UDST policy on the NTEP may have led to this decreasing trend in RIF and INH resistance observed in the study period. The increase in low-level INH resistance mutation inhA-c-15t may be associated with ethionamide/prothionamide resistance, and this should be taken into account when designing DR-TB regimen.

DOI: 10.5588/ijtld.21.0455
PMID: 35505474 [Indexed for MEDLINE]

29**. Evaluation of TBMDR® and XDRA® for the detection of multidrug resistant and pre-extensively drug resistant tuberculosis.**

J Clin Tuberc Other Mycobact Dis. 2022 Feb 9;27:100303. doi: 10.1016/j.jctube.2022.100303. eCollection 2022 May.

Cho E(1), Lee SJ(2), Lim J(2), Kim DS(2), Kim N(2), Park HO(2), Lee JI(1), Son E(1), Cho SN(1), Aung WW(3), Seok Lee J(1).

This study evaluated the diagnostic performance of the AccuPower® TB&MDR Real-Time PCR (TBMDR®) and AccuPower® XDR-TB Real-Time PCR Kit-A (XDRA®) to detect multidrug-resistant (MDR-TB) and pre-extensively drug-resistant tuberculosis (pre-XDR-TB) in comparison with phenotypic drug susceptibility testing (DST) using MGIT 960 on 234 clinical Mycobacterium tuberculosis isolates. Discrepant results were confirmed by direct-sequencing. Sensitivity and specificity of TBMDR and XDRA for cultured isolates were 81.2% and 95.8% for isoniazid (INH) resistance, 95.7% and 95.7% for rifampicin (RIF) resistance, 84.1% and 99.1% for fluoroquinolone (FQ) resistance, and 67.4% and 100% for second-line injectables resistance. The sensitivities of each drug were equivalent to other molecular DST methods. High concordance was observed when compared to direct-sequencing. We also found that TBMDR and XDRA assays can detect INH, RIF and FQ resistance in isolates with low level resistance-associated mutations which were missed by phenotypic DST. Our study showed TBMDR and XDRA assays could be the useful tools to detect MDR-TB and pre-XDR-TB.

DOI: 10.1016/j.jctube.2022.100303
PMCID: PMC8857659
PMID: 35243010

30**. Whole-genome sequencing of Mycobacterium tuberculosis from Cambodia.**

Sci Rep. 2022 May 11;12(1):7693. doi: 10.1038/s41598-022-10964-9.

Edokimov K(1), Yamada Y(1), Dary C(2), Miow QH(3), Hsu LY(1), Ong RT(4), Saphonn V(5).

Cambodia has one of the highest tuberculosis (TB) incidence rates in the WHO Western Pacific region. Remarkably though, the prevalence of multidrug-resistant TB (MDR-TB) remains low. We explored the genetic diversity of Mycobacterium tuberculosis (MTB) circulating in this unique setting using whole-genome sequencing (WGS). From October 2017 until January 2018, we collected one hundred sputum specimens from consenting adults older than 21 years of age, newly diagnosed with bacteriologically confirmed TB in 3 districts of Phnom Penh and Takeo provinces of Cambodia before they commence on their TB treatment, where eighty MTB isolates were successfully cultured and sequenced. Majority of the isolates belonged to Lineage 1 (Indo-Oceanic) (69/80, 86.25%), followed by

Lineage 2 (East Asian) (10/80, 12.5%) and Lineage 4 (Euro-American) (1/80, 1.25%). Phenotypic resistance to both streptomycin and isoniazid was found in 3 isolates (3/80, 3.75%), while mono-resistance to streptomycin and isoniazid was identical at 2.5% (N = 2 each). None of the isolates tested was resistant to either rifampicin or ethambutol. The specificities of genotypic prediction for resistance to all drugs tested were 100%, while the sensitivities of genotypic resistance predictions to isoniazid and streptomycin were lower at 40% (2/5) and 80% (4/5) respectively. We identified 8 clusters each comprising of two to five individuals all residing in the Takeo province, making up half (28/56, 50%) of all individuals sampled in the province, indicating the presence of multiple ongoing transmission events. All clustered isolates were of Lineage 1 and none are resistant to any of the drugs tested. This study while demonstrating the relevance and utility of WGS in predicting drug resistance and inference of disease transmission, highlights the need to increase the representation of genotype-phenotype TB data from low and middle income countries in Asia and Africa to improve the accuracies for prediction of drug resistance.

DOI: 10.1038/s41598-022-10964-9
PMCID: PMC9095694
PMID: 35562174 [Indexed for MEDLINE]

31. Systematic TB screening using WHO radiograph categorisation and care outcomes.

Int J Tuberc Lung Dis. 2022 May 1;26(5):419-425. doi: 10.5588/ijtld.21.0618.

Jittimanee S(1), Namonta A(2), Charuenporn C(3).

BACKGROUND: An appropriate screening approach and quality care are crucial for TB programmes in prisons. This study assessed crude TB prevalence, accuracy of the screening methods and treatment outcomes in a Thai prison.METHOD: This was a retrospective analysis of findings from a mass CXR screening conducted among incarcerated people in July 2017. Digital radiographs were forwarded to a chest physician to read and classify in six categories using WHO categorisation. CXR with significant Categories 3 (no active TB), 4 (not TB), 5 (TB) and 6 (unclassified) abnormalities were eligible for sputum microscopy and Xpert testing. A screening questionnaire locally known as TB-P1 was used for case management. Patients with TB received care in the prison.RESULTS: Of 2,382 prisoners screened, 6.3% had CXR Categories 3-6. Crude prevalence of bacteriologically confirmed TB was 1,133/100,000 (95% CI 748.3-1644.9). The screening´s sensitivity was 96.3% based on CXR Category 5 and 22.2% using TB-P1. Treatment success rates in drug-susceptible and drug-resistant TB patients were respectively 66.7% and 33.3%.CONCLUSION: The WHO radiograph categorisation could

be used to screen for TB in the field and may be applied in artificial intelligence for interpreting CXR; screening questionnaires are not effective in prison environments. Nonetheless, low treatment success rates remained a challenge.

DOI: 10.5588/ijtld.21.0618
PMID: 35505479 [Indexed for MEDLINE]

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

J Leukoc Biol. 2022 May;111(5):1021-1029. doi: 10.1002/JLB.4A0221-119RR. Epub 2021 Sep 17.

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 [Indexed for MEDLINE]

33. **Association between Mycobacterium tuberculosis genotype and diabetes mellitus/hypertension: a molecular study.**

BMC Infect Dis. 2022 Apr 24;22(1):401. doi: 10.1186/s12879-022-07344-z.

Guo S(1)(2), Lei S(#)(1), Palittapongarnpim P(3)(4), McNeil E(2), Chaiprasert A(5), Li J(#)(1), Chen H(1), Ou W(6), Surachat K(7)(8), Qin W(6), Zhang S(9), Luo R(9), Chongsuvivatwong V(#)(10).

BACKGROUND: A paucity of studies focused on the genetic association that tuberculosis (TB) patients with non-communicable diseases (NCDs) are more likely to be infected with Mycobacterium tuberculosis (MTB) with more potent virulence on anti-TB drug resistance than those without NCDs. The study aimed to document the predominant genotype, determine the association between MTB genotypes and NCD status and drug resistance.
METHODS: We conducted a molecular study in 105 TB patients based on a cross-sectional study focused on the comorbid relationship between chronic conditions and TB among 1773 subjects from September 1, 2019 to August 30, 2020 in Guizhou, China. The participants were investigated through face-to-face interviews, followed by NCDs screening. The DNA of MTB isolates was extracted prior to genotyping using 24 loci MIRU-VNTR. The subsequent evaluations were performed by phylogenetic trees, combined with tests of statistical power, Chi-square or Fisher and multivariate logistic regression analysis.
RESULTS: The Beijing family of Lineage 2 (East Asia) was the predominant genotype accounting for 43.8% (46/105), followed by Lineage 4 (Euro-America) strains, including Uganda I (34.3%, 36/105), and the NEW-1 (9.5%, 10/105). The proportion of Beijing strain in patients with and without NCDS was 28.6% (8/28) and 49.4% (38/77), respectively, with a statistical power test value of 24.3%. No significant association was detected between MTB genotype and NCD status. A low clustering rate (2.9%) was identified, consisting of two clusters. The rates of global, mono-, poly- and multi-drug resistance were 16.2% (17/105), 14.3% (15/105), 1.0% (1/105) and 4.8% (5/105), respectively. The drug-resistant rates of rifampicin, isoniazid, and streptomycin, were 6.7% (7/105), 11.4% (12/105) and 5.7% (6/105), respectively. Isoniazid resistance was significantly associated with the Beijing genotype of Lineage 2 (19.6% versus 5.1%).
CONCLUSIONS: The Lineage 2 East Asia/Beijing genotype is the dominant genotype of the local MTB with endogenous infection preponderating. Not enough evidence is detected to support the association between the MTB genotype and diabetes/hypertension. Isoniazid resistance is associated with the Lineage 2 East Asia/Beijing strain.

DOI: 10.1186/s12879-022-07344-z
PMCID: PMC9035274
PMID: 35462543 [Indexed for MEDLINE]

34. **Epigenetic changes in Mycobacterium tuberculosis and its host provide potential targets or biomarkers for drug discovery and clinical diagnosis.**

Pharmacol Res. 2022 May;179:106195. doi: 10.1016/j.phrs.2022.106195. Epub 2022 Mar 29.

Sui J(1), Qiao W(2), Xiang X(1), Luo Y(3).

Tuberculosis infection caused by the contagious pathogen Mycobacterium tuberculosis (MTB) is one of the ancient diseases in the world. The problem of drug resistance is a difficulty in tuberculosis treatment. MTB engendered epigenetic changes play vital parts in escaping the host immune response and bring about the persistence as well as bacterial expansion. This article describes the epigenetic changes that occur in the pathogen MTB and its host during infection, including DNA methylation, histone modification and microRNA, and summarizes their research progress in drug discovery and tuberculosis diagnosis, providing new ideas and strategies to combat against drug-resistant tuberculosis.

DOI: 10.1016/j.phrs.2022.106195
PMID: 35364247

35**. Prediction of Mycobacterium tuberculosis drug resistance by nucleotide MALDI-TOF-MS.**

Int J Infect Dis. 2022 May 4;121:47-54. doi: 10.1016/j.ijid.2022.04.061. Online ahead of print.

Wu X(1), Tan G(2), Yang J(1), Guo Y(1), Huang C(3), Sha W(4), Yu F(5).

OBJECTIVES: To evaluate the performance of nucleotide matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF-MS) in predicting the drug resistance of Mycobacterium tuberculosis.
METHODS: A total of 115 rifampin-resistant and 53 rifampin-susceptible tuberculosis (TB) clinical isolates were randomly selected from TB strains stored at -80°C in the clinical laboratory of Shanghai Pulmonary Hospital. Nucleotide MALDI-TOF-MS was performed to predict the drug resistance using phenotypic susceptibility as the gold standard.
RESULTS: The overall assay sensitivities and specificities of nucleotide MALDI-TOF-MS were 92.2% and 100.0% for rifampin, 90.9% and 98.6% for isoniazid, 71.4% and 81.2% for ethambutol, 85.1% and 93.1% for streptomycin, 94.0% and 100.0% for amikacin, 77.8% and 99.3% for kanamycin, 75.0% and 93.3% for

ofloxacin, and 75.0% and 93.3% for moxifloxacin. The concordances between nucleotide MALDI-TOF-MS antimicrobial susceptibility testing (AST) and phenotypic AST were 94.6% (rifampin), 90.1% (isoniazid), 79.2% (ethambutol), 89.9% (streptomycin), 99.4% (amikacin), 97.0% (kanamycin), 88.1% (ofloxacin), and 88.0% (moxifloxacin).
CONCLUSION: Nucleotide MALDI-TOF-MS could be a promising tool for rapid detection of Mycobacterium tuberculosis drug sensitivity to rifampin, isoniazid, ethambutol, streptomycin, amikacin, kanamycin, ofloxacin, and moxifloxacin.

DOI: 10.1016/j.ijid.2022.04.061
PMID: 35523300

36**. Whole-genome sequencing for surveillance of tuberculosis drug resistance and determination of resistance level in China.**

Clin Microbiol Infect. 2022 May;28(5):731.e9-731.e15. doi: 10.1016/j.cmi.2021.09.014. Epub 2021 Sep 30.

Liu D(1), Huang F(2), Zhang G(3), He W(2), Ou X(2), He P(2), Zhao B(2), Zhu B(4), Liu F(4), Li Z(4), Liu C(2), Xia H(2), Wang S(2), Zhou Y(2), Walker TM(5), Liu L(3), Crook DW(5), Zhao Y(6).

OBJECTIVES: Phenotypic drug susceptibility testing for prediction of tuberculosis (TB) drug resistance is slow and unreliable, limiting individualized therapy and monitoring of national TB data. Our study evaluated whole-genome sequencing (WGS) for its predictive accuracy, use in TB drug-resistance surveillance and ability to quantify the effects of resistance-associated mutations on MICs of anti-TB drugs.
METHODS: We used WGS to measure the susceptibility of 4880 isolates to ten anti-TB drugs; for pyrazinamide, we used BACTEC MGIT 960. We determined the accuracy of WGS by comparing the prevalence of drug resistance, measured by WGS, with the true prevalence, determined by phenotypic susceptibility testing. We used the Student-Newman-Keuls test to confirm MIC differences of mutations.
RESULTS: Resistance to isoniazid, rifampin and ethambutol was highly accurately predicted with at least 92.92% (95% confidence interval [CI], 88.19-97.65) sensitivity, resistance to pyrazinamide with 50.52% (95% CI, 40.57-60.47) sensitivity, and resistance to six second-line drugs with 85.05% (95% CI, 80.27-89.83) to 96.01% (95% CI, 93.89-98.13) sensitivity. The rpoB S450L, katG S315T and gyrA D94G mutations always confer high-level resistance, while rpoB L430P, rpoB L452P, fabG1 C-15T and embB G406S often confer low-level resistance or sub-epidemiological cutoff (ECOFF) MIC elevation.
CONCLUSION: WGS can predict phenotypic susceptibility with high accuracy and

could be a valuable tool for drug-resistance surveillance and allow the detection of drug-resistance level; It can be an important approach in TB drug-resistance surveillance and for determining therapeutic schemes.

DOI: 10.1016/j.cmi.2021.09.014
PMID: 34600118 [Indexed for MEDLINE]

37**. Analysis of efficacy and safety of linezolid-based chemotherapeutic regimens for patients with postoperative multidrug-resistant spinal tuberculosis.**

Int J Infect Dis. 2022 May;118:264-269. doi: 10.1016/j.ijid.2022.03.020. Epub 2022 Mar 24.

Qiao J(1), Yang L(2), Feng J(2), Dai X(3), Xu F(3), Xia P(4).

OBJECTIVES: The study aimed to explore the efficacy and safety of linezolid-based chemotherapeutic regimens for patients with postoperative multidrug-resistant spinal tuberculosis.
METHODS: The randomized controlled study included 50 Mycobacterium tuberculosis culture or pathological-confirmed multidrug resistant tuberculosis patients who received spinal surgery from January 2018 to February 2020. Twenty-five patients were assigned to the control group and the study group, respectively. Random number method was used for patient allocation and they were treated with levofloxacin, pyrazinamide, thioisonicotinamide enteric-coated tablet, amikacin sulfate injection, and sodium p-amino salicylate injection, accompanied by linezolid or not.
RESULTS: The overall effective rate of the study group was higher than that of the control group (88.00% vs 64.00%, P<0.05). The severity of pain at 3 and 6 months postoperatively was lower in the study group than that in the control group (P<0.05). Postoperatively, the study group had higher bone graft fusion rate, shorter mean bone graft fusion time, and higher paraspinal cyst absorption rate than the control group (P<0.05). Postoperatively, the study group had lower levels of PCT, ESR, and CRP than the control group (P <0.05). All patients had normal hepatic and renal function, and no statistical difference of adverse effects between 2 groups were found.
CONCLUSIONS: Linezolid-based chemotherapeutic regimens can effectively treat patients with postoperative multidrug-resistant spinal tuberculosis but have higher rates of adverse reactions.

DOI: 10.1016/j.ijid.2022.03.020

PMID: 35339715 [Indexed for MEDLINE]

38. **Essential tuberculosis medicines and health outcomes in countries with a national essential medicines list.**

J Clin Tuberc Other Mycobact Dis. 2022 Feb 23;27:100305. doi: 10.1016/j.jctube.2022.100305. eCollection 2022 May.

Maraj D(1), Steiner L(1), Persaud N(2).

BACKGROUND: Tuberculosis (TB) remains a major cause of morbidity and mortality globally despite effective treatments. Along with high-quality health services, essential medicines are a key tool in curbing TB related mortality. Examining relationships between listing TB medicines on national essential medicines lists (NEMLs) and population health outcomes related to amenable mortality is one way to assess TB care.
METHODS: In this cross-sectional study of 137 countries, we used linear regression to examine the relationship between the number of TB medicines listed on NEMLs and TB related mortality while controlling for country income, region and TB burden.
RESULTS: Most countries listed essential TB medicines to treat latent, drug-sensitive and disseminated TB but few listed enough for multi-drug resistant TB (MDR-TB) therapy. The total number of TB medicines listed ranged from 1 to 29 (median: 19, interquartile range: 15 to 22). Over 75% of the variation in health outcomes were explained by the number of TB medicines listed, gross domestic product (GDP) per capita, region and high-burden MDR-TB status. The number of TB medicines listed was not associated with TB mortality.
CONCLUSION: Most countries list essential TB treatments and the variation in TB outcomes is explained by other factors such as GDP.

DOI: 10.1016/j.jctube.2022.100305
PMCID: PMC8924688
PMID: 35308809

39. **Recurrent pulmonary tuberculosis after treatment success: a population-based retrospective study in China.**

Clin Microbiol Infect. 2022 May;28(5):684-689. doi: 10.1016/j.cmi.2021.09.022. Epub 2021 Sep 30.

Ruan QL(1), Yang QL(1), Sun F(1), Liu W(2), Shen YJ(1), Wu J(1), Jiang N(3), Zhou JY(1), Shao LY(4), Zhang WH(5).

Comment in
Clin Microbiol Infect. 2022 May;28(5):631-633.

OBJECTIVES: Post-treatment recurrence remains a challenge for the global control of tuberculosis (TB). This study investigated longitudinal data on pulmonary TB recurrence rates and risk factors for recurrence among successfully treated smear-positive tuberculosis cases in China.
METHODS: Between 1st January 2009 and 31st December 2016 we evaluated 33 441 treatment-naïve patients diagnosed with sputum-smear-positive, non-multidrug-resistant TB in Hangzhou, China. We included the data of 9828 patients with TB who were treated successfully.
RESULTS: A total of 4.9% of the cases were recurrent (479/9828), identified within a median observation period lasting 1565 days. Altogether, 51.1% (245/479) of the recurrences occurred within 1 year. The cumulative 2- and 5-year recurrence rates were 3.90% (95% confidence interval (CI) 3.3-4.5%) and 5.4% (95%CI 4.8-6.0%), respectively. Prolonged treatment (over 7 months) occurred in 64.7% (6363/9828), with a median treatment duration of 242 days (interquartile range 195-348 days). Male sex (adjusted hazard ratio (aHR) (95%CI) 1.61 (1.30-2.00), p < 0.001), age 60 years old or older (aHR (95%CI) 2.03 (1.70-2.44), p < 0.001), pulmonary cavity (aHR (95%CI) 1.51 (1.25-1.82), p < 0.001) and sputum positivity at 2 months (aHR (95%CI) 1.39 (1.05-1.81), p 0.02) all increased the risk of TB recurrence. Prolonged treatment was associated with reduced TB recurrence (aHR (95%CI) 0.73 (0.61-0.88), p 0.001).
CONCLUSIONS: Recurrence remains a problem for successfully treated patients with sputum-smear-positive pulmonary TB, especially those with independent risk factors. Further analysis of prolonged treatment is required.

DOI: 10.1016/j.cmi.2021.09.022
PMID: 34601149 [Indexed for MEDLINE]

40**. Multidrug-resistant tuberculosis control in Rwanda overcomes a successful clone that causes most disease over a quarter century.**

J Clin Tuberc Other Mycobact Dis. 2022 Jan 24;27:100299. doi: 10.1016/j.jctube.2022.100299. eCollection 2022 May.

Ngabonziza JCS(1)(2)(3), Rigouts L(2)(4), Torrea G(2), Decroo T(5)(6), Kamanzi E(1), Lempens P(2)(4), Rucogoza A(1), Habimana YM(7), Laenen L(8), Niyigena BE(1), Uwizeye C(2), Ushizimpumu B(1), Mulders W(2), Ivan E(1), Tzfadia O(2), Muvunyi CM(3), Migambi P(6), Andre E(2)(8)(9), Mazarati JB(10), Affolabi D(11), Umubyeyi AN(12), Nsanzimana S(13), Portaels F(2), Gasana M(7), de Jong BC(2),

Meehan CJ(2)(14).

SUMMARY BACKGROUND: Multidrug-resistant (MDR) tuberculosis (TB) poses an important challenge in TB management and control. Rifampicin resistance (RR) is a solid surrogate marker of MDR-TB. We investigated the RR-TB clustering rates, bacterial population dynamics to infer transmission dynamics, and the impact of changes to patient management on these dynamics over 27 years in Rwanda.
METHODS: We analysed whole genome sequences of a longitudinal collection of nationwide RR-TB isolates. The collection covered three important periods: before programmatic management of MDR-TB (PMDT; 1991-2005), the early PMDT phase (2006-2013), in which rifampicin drug-susceptibility testing (DST) was offered to retreatment patients only, and the consolidated phase (2014-2018), in which all bacteriologically confirmed TB patients had rifampicin DST done mostly via Xpert MTB/RIF assay. We constructed clusters based on a 5 SNP cut-off and resistance conferring SNPs. We used Bayesian modelling for dating and population size estimations, TransPhylo to estimate the number of secondary cases infected by each patient, and multivariable logistic regression to assess predictors of being infected by the dominant clone.
RESULTS: Of 308 baseline RR-TB isolates considered for transmission analysis, the clustering analysis grouped 259 (84.1%) isolates into 13 clusters. Within these clusters, a single dominant clone was discovered containing 213 isolates (82.2% of clustered and 69.1% of all RR-TB), which we named the "Rwanda Rifampicin-Resistant clone" (R3clone). R3clone isolates belonged to Ugandan sub-lineage 4.6.1.2 and its rifampicin and isoniazid resistance were conferred by the Ser450Leu mutation in rpoB and Ser315Thr in katG genes, respectively. All R3clone isolates had Pro481Thr, a putative compensatory mutation in the rpoC gene that likely restored its fitness. The R3clone was estimated to first arise in 1987 and its population size increased exponentially through the 1990s', reaching maximum size (∼84%) in early 2000 s', with a declining trend since 2014. Indeed, the highest proportion of R3clone (129/157; 82·2%, 95%CI: 75·3-87·8%) occurred between 2000 and 13, declining to 64·4% (95%CI: 55·1-73·0%) from 2014 onward. We showed that patients with R3clone detected after an unsuccessful category 2 treatment were more likely to generate secondary cases than patients with R3clone detected after an unsuccessful category 1 treatment regimen.
CONCLUSIONS: RR-TB in Rwanda is largely transmitted. Xpert MTB/RIF assay as first diagnostic test avoids unnecessary rounds of rifampicin-based TB treatment, thus preventing ongoing transmission of the dominant R3clone. As PMDT was intensified and all TB patients accessed rifampicin-resistance testing, the nationwide R3clone burden declined. To our knowledge, our findings provide the first evidence supporting the impact of universal DST on the transmission of RR-TB.

DOI: 10.1016/j.jctube.2022.100299
PMCID: PMC8802117
PMID: 35146133

41. **First report of whole-genome analysis of an extensively drug-resistant Mycobacterium tuberculosis clinical isolate with bedaquiline, linezolid and clofazimine resistance from Uganda.**

Antimicrob Resist Infect Control. 2022 May 12;11(1):68. doi: 10.1186/s13756-022-01101-2.

Kabahita JM(1), Kabugo J(1), Kakooza F(2), Adam I(1), Guido O(1), Byabajungu H(1), Namutebi J(1), Namaganda MM(3), Lutaaya P(1), Otim J(4), Kakembo FE(5), Kanyerezi S(5), Nabisubi P(5), Sserwadda I(3), Kasule GW(1), Nakato H(1), Musisi K(1), Oola D(1), Joloba ML(1)(3), Mboowa G(6)(7).

BACKGROUND: Uganda remains one of the countries with the highest burden of TB/HIV. Drug-resistant TB remains a substantial challenge to TB control globally and requires new strategic effective control approaches. Drug resistance usually develops due to inadequate management of TB patients including improper treatment regimens and failure to complete the treatment course which may be due to an unstable supply or a lack of access to treatment, as well as patient noncompliance.
METHODS: Two sputa samples were collected from Xpert MTB/RIF® assay-diagnosed multi-drug resistant tuberculosis (MDR-TB) patient at Lira regional referral hospital in northern Uganda between 2020 and 2021 for comprehensive routine mycobacterial species identification and drug susceptibility testing using culture-based methods. Detection of drug resistance-conferring genes was subsequently performed using whole-genome sequencing with Illumina MiSeq platform at the TB Supranational Reference Laboratory in Uganda.
RESULTS: In both isolates, extensively drug-resistant TB (XDR-TB) was identified including resistance to Isoniazid (katG p.Ser315Thr), Rifampicin (rpoB p.Ser450Leu), Moxifloxacin (gyrA p.Asp94Gly), Bedaquiline (Rv0678 Glu49fs), Clofazimine (Rv0678 Glu49fs), Linezolid (rplC Cys154Arg), and Ethionamide (ethA c.477del). Further analysis of these two high quality genomes revealed that this 32 years-old patient was infected with the Latin American Mediterranean TB strain (LAM).
CONCLUSIONS: This is the first identification of extensively drug-resistant Mycobacterium tuberculosis clinical isolates with bedaquiline, linezolid and clofazimine resistance from Uganda. These acquired resistances were because of non-adherence as seen in the patient's clinical history. Our study also strongly highlights the importance of combating DR-TB in Africa through implementing next generation sequencing that can test resistance to all drugs while providing a

faster turnaround time. This can facilitate timely clinical decisions in managing MDR-TB patients with non-adherence or lost to follow-up.

DOI: 10.1186/s13756-022-01101-2
PMCID: PMC9102340
PMID: 35550202 [Indexed for MEDLINE]

42**. A case of primary multidrug-resistant pulmonary tuberculosis with high minimum inhibitory concentration value for bedaquiline.**

J Infect Chemother. 2022 May 9:S1341-321X(22)00142-8. doi: 10.1016/j.jiac.2022.04.028. Online ahead of print.

Kobayashi M(1), Motoki Y(2), Yamagishi T(3), Hirano H(3), Nonaka M(3), Aono A(4), Mitarai S(4), Saito T(3).

Bedaquiline is a new ATP synthesis inhibitor developed as an anti-tuberculosis agent. It has resistance-associated variants (RAV), regardless of preceding bedaquiline exposure. Herein, we describe the case of a patient with multidrug-resistant tuberculosis (MDR-TB) who had no history of bedaquiline therapy but presented a relatively high minimum inhibitory concentration (MIC) of bedaquiline (1 μg/mL). Whole genome sequencing revealed a mutation in the resistance-associated gene Rv0678. The patient was first treated with a five-drug regimen (bedaquiline, delamanid, levofloxacin, cycloserine, and amikacin), which induced negative sputum culture conversion. Despite the successful treatment outcome, several questions remain regarding the efficacy of bedaquiline in this patient. Bedaquiline is an indispensable drug for MDR-TB treatment, but its clinical efficiency in the presence of Rv0678 mutations remains unclear. Therefore, evaluating the MIC of bedaquiline even in patients without a history of bedaquiline use is important for therapeutic regimen selection and may emphasize the importance of therapeutic drug monitoring in cases of bedaquiline RAV.

DOI: 10.1016/j.jiac.2022.04.028
PMID: 35550867

43**. A Score to Predict the Risk of Major Adverse Drug Reactions Among Multi-Drug Resistant Tuberculosis Patients in Southern Ethiopia, 2014-2019.**

Infect Drug Resist. 2022 Apr 21;15:2055-2065. doi: 10.2147/IDR.S351076. eCollection 2022.

Bogale L(1), Tenaw D(2), Tsegaye T(1), Abdulkadir M(1), Akalu TY(3).

BACKGROUND: Adverse events (AE) contribute to poor drug adherence and withdrawal, which contribute to a low treatment success rate. AE are commonly reported among multi-drug resistance tuberculosis (MDR-TB) patients in Ethiopia. However, predictors of AE among MDR-TB patients were limited in Ethiopia. Thus, the current study aimed to develop and validate a score to predict the risks of major AE among MDR-TB patients in Southern Ethiopia.
METHODS: A retrospective follow-up study design was employed among MDR-TB patients from 2014-2019 in southern Ethiopia at selected hospitals. A least absolute shrinkage and selection operator algorithm was used to select the most potent predictors of the outcome. The adverse event risk score was built based on the multivariable logistic regression analysis. Discriminatory power and calibration were checked to evaluate the performance of the model. Bootstrapping method with 100 repetitions was used for internal model validation.
RESULTS: History of baseline khat use, long-term drug regimen use, and having coexisting disorders (co-morbidity) were predictors of AEs. The score has a satisfactory discriminatory power (AUC = 0.77, 95% CI: 0.68, 0.82) and a modest calibration (Prob > chi2 = 0.2043). It was found to have the same c-statistics after validation by bootstrapping method of 100 repetitions with replacement.
CONCLUSION: A history of baseline khat use, co-morbidity, and long-term drug regimen use are helpful to predict individual risk of major adverse events in MDR-TB patients with a satisfactory degree of accuracy (AUC = 0.77).

DOI: 10.2147/IDR.S351076
PMCID: PMC9037729
PMID: 35480059

44. **Susceptibility of β-lactam antibiotics and genetic mutation of drug-resistant Mycobacterium tuberculosis isolates in Korea.**

Tuberc Respir Dis (Seoul). 2022 May 19. doi: 10.4046/trd.2021.0175. Online ahead of print.

Park S(1), Jung J(1), Kim J(1), Han SB(2), Ryoo S(1).

BACKGROUND: Mycobacterium tuberculosis (Mtb) is resistant to the β-lactam antibiotics due to a non-classical transpeptidase in the cell wall with β-lactamase activity. A recent study showed that meropenem combined with a

β-lactamase inhibitor clavulanate, was effective in MDR and XDR tuberculosis (TB). However, clavulanate can only be used in drugs containing amoxicillin in Korea. In this study, we investigated the susceptibility and genetic mutations of drug-resistant Mtb isolates to amoxicillin-clavulanate and meropenem-clavulanate to improve the diagnosis and treatment of drug-resistant TB patients.
METHODS: The minimum inhibitory concentration (MIC) of amoxicillin-clavulanate and meropenem-clavulanate was examined by resazurin microtiter assay. We used 82 MDR and 40 XDR strains isolated in Korea and two reference laboratory strains. Mutations of drug targets blaC, blaI, ldtA, ldtB, dacB2, and crfA were analyzed by PCR and DNA sequencing.
RESULTS: The MIC90 values of amoxicillin and meropenem with clavulanate in drug-resistant Mtb isolates were 64 and 16, respectively. Gene mutations related to amoxicillin/clavulanate and meropenem/clavulanate resistance could not be identified, but T448G mutation of was found in the blaC gene related to β-lactam antibiotics high susceptibility.
CONCLUSION: Our results provide clinical consideration of β-lactams in treating drug-resistant TB and potential molecular markers of amoxicillin-clavulanate and meropenem-clavulanate susceptibility.

DOI: 10.4046/trd.2021.0175
PMID: 35586904

45**. Spiropyrimidinetrione DNA Gyrase Inhibitors with Potent and Selective Antituberculosis Activity.**

J Med Chem. 2022 May 12;65(9):6903-6925. doi: 10.1021/acs.jmedchem.2c00266. Epub 2022 May 2.

Govender P(1), Müller R(1), Singh K(1), Reddy V(1), Eyermann CJ(1), Fienberg S(1), Ghorpade SR(1), Koekemoer L(2), Myrick A(2), Schnappinger D(3), Engelhart C(3), Meshanni J(3), Byl JAW(4), Osheroff N(4)(5)(6), Singh V(1)(2), Chibale K(1)(2), Basarab GS(1)(7).

New antibiotics with either a novel mode of action or novel mode of inhibition are urgently needed to overcome the threat of drug-resistant tuberculosis (TB). The present study profiles new spiropyrimidinetriones (SPTs), DNA gyrase inhibitors having activity against drug-resistant Mycobacterium tuberculosis (Mtb), the causative agent of TB. While the clinical candidate zoliflodacin has progressed to phase 3 trials for the treatment of gonorrhea, compounds herein demonstrated higher inhibitory potency against Mtb DNA gyrase (e.g., compound 42 with IC50 = 2.0) and lower Mtb minimum inhibitor concentrations (0.49 μM for 42). Notably, 42 and analogues showed selective Mtb activity relative to representative Gram-positive and Gram-negative bacteria. DNA gyrase inhibition

was shown to involve stabilization of double-cleaved DNA, while on-target activity was supported by hypersensitivity against a gyrA hypomorph. Finally, a docking model for SPTs with Mtb DNA gyrase was developed, and a structural hypothesis was built for structure-activity relationship expansion.

DOI: 10.1021/acs.jmedchem.2c00266
PMID: 35500229 [Indexed for MEDLINE]

46. **Treatment outcomes of multi-drug resistant tuberculosis patients with or without human immunodeficiency virus co-infection in Africa and Asia: Systematic review and meta-analysis.**

Ann Med Surg (Lond). 2022 May 11;78:103753. doi: 10.1016/j.amsu.2022.103753. eCollection 2022 Jun.

Kajogoo VD(1), Lalashowi J(2), Olomi W(2), Atim MG(3), Assefa DG(4), Sabi I(2).

BACKGROUND: Treatment outcomes of multidrug resistant tuberculosis (MDRTB) is a challenge, especially in resource limited settings. The aim of this study was to compare whether Human Immune Virus (HIV) has influence on the treatment outcomes of MDRTB among patients in Africa and Asia.
METHODS: Studies were searched from PubMed, Google scholar, African Journals online, EBSCOhost and CENTRAL from year 2000 until January 2021. The participants in the studies were reported of using MDRTB treatment regimen and also included those with HIV. Studies published before 2000 were excluded. Quality of the review was assessed by AMSTEL 2 criteria. The Mantel- Haenszel random effects method was used for the analysis, with risk ratio (RR) as an effect estimate, with 95% confidence interval and using Stata 14 software.
RESULTS: Nine studies were included in the meta-analysis. Treatment success was low in HIV negative participants (RR 0.62, 95% CI 0.58-0.67). However, death was higher in the HIV co-infected participants. (RR 1.35, 95% CI 1.25-1.45). There was no significant difference in treatment failure among patients with or without HIV. (RR 1.08, 95% CI 0.97-1.20). Consistently, no significant difference was found in lost to follow up (LTF) between the two groups (RR 1.07, 95% CI 0.93-1.20).
CONCLUSION: Treatment success was lower for the MDRTB and HIV co-infections. No significant difference has been found on other outcomes like failure and lost to follow up between patients with HIV co-infected and HIV negative group. The study limitations are that we had only 2 studies representing Asia, and this could have affected the outcome of results. There is need for interventions to improve treatment success in the HIV co-infected group.
OTHER: The protocol was registered in International prospective register of systematic reviews (PROSPERO), ID: CRD42021247883. There was no funding for the review.

DOI: 10.1016/j.amsu.2022.103753
PMCID: PMC9121254
PMID: 35600168

47. **In vitro Evaluation of Isoniazid Derivatives as Potential Agents Against Drug-Resistant Tuberculosis.**

Front Pharmacol. 2022 May 4;13:868545. doi: 10.3389/fphar.2022.868545. eCollection 2022.

Marquês JT(1), Frazão De Faria C(1), Reis M(1)(2), Machado D(3), Santos S(1), Santos MDS(1), Viveiros M(3), Martins F(1), De Almeida RFM(1).

The upsurge of multidrug-resistant tuberculosis has toughened the challenge to put an end to this epidemic by 2030. In 2020 the number of deaths attributed to tuberculosis increased as compared to 2019 and newly identified multidrug-resistant tuberculosis cases have been stably close to 3%. Such a context stimulated the search for new and more efficient antitubercular compounds, which culminated in the QSAR-oriented design and synthesis of a series of isoniazid derivatives active against Mycobacterium tuberculosis. From these, some prospective isonicotinoyl hydrazones and isonicotinoyl hydrazides are studied in this work. To evaluate if the chemical derivatizations are generating compounds with a good performance concerning several in vitro assays, their cytotoxicity against human liver HepG2 cells was determined and their ability to bind human serum albumin was thoroughly investigated. For the two new derivatives presented in this study, we also determined their lipophilicity and activity against both the wild type and an isoniazid-resistant strain of Mycobacterium tuberculosis carrying the most prevalent mutation on the katG gene, S315T. All compounds were less cytotoxic than many drugs in clinical use with IC50 values after a 72 h challenge always higher than 25 µM. Additionally, all isoniazid derivatives studied exhibited stronger binding to human serum albumin than isoniazid itself, with dissociation constants in the order of 10-4-10-5 M as opposed to 10-3 M, respectively. This suggests that their transport and half-life in the blood stream are likely improved when compared to the parent compound. Furthermore, our results are a strong indication that the N' = C bond of the hydrazone derivatives of INH tested is essential for their enhanced activity against the mutant strain of M. tuberculosis in comparison to both their reduced counterparts and INH.

DOI: 10.3389/fphar.2022.868545
PMCID: PMC9114799
PMID: 35600870

48. **Tapping into the antitubercular potential of 2,5-dimethylpyrroles: A structure-activity relationship interrogation.**

Eur J Med Chem. 2022 Apr 21;237:114404. doi: 10.1016/j.ejmech.2022.114404. Online ahead of print.

Semenya D(1), Touitou M(1), Masci D(1), Ribeiro CM(2), Pavan FR(2), Dos Santos Fernandes GF(1), Gianibbi B(3), Manetti F(3), Castagnolo D(4).

An exploration of the chemical space around a 2,5-dimethylpyrrole scaffold of antitubercular hit compound 1 has led to the identification of new derivatives active against Mycobacterium tuberculosis and multidrug-resistant clinical isolates. Analogues incorporating a cyclohexanemethyl group on the methyleneamine side chain at C3 of the pyrrole core, including 5n and 5q, exhibited potent inhibitory effects against the M. tuberculosis strains, substantiating the essentiality of the moiety to their antimycobacterial activity. In addition, selected derivatives showed promising cytotoxicity profiles against human pulmonary fibroblasts and/or murine macrophages, proved to be effective in inhibiting the growth of intracellular mycobacteria, and elicited either bactericidal effects, or bacteriostatic activity comparable to 1. Computational studies revealed that the new compounds bind to the putative target, MmpL3, in a manner similar to that of known inhibitors BM212 and SQ109.

DOI: 10.1016/j.ejmech.2022.114404
PMID: 35486992

49. **A modeling-based proposal for safe and efficacious reintroduction of bedaquiline after dose interruption: A population pharmacokinetics study.**

CPT Pharmacometrics Syst Pharmacol. 2022 May;11(5):628-639. doi: 10.1002/psp4.12768. Epub 2022 Feb 16.

Keutzer L(1), Akhondipour Salehabad Y(1), Davies Forsman L(2)(3), Simonsson USH(1).

Bedaquiline (BDQ) is recommended for treatment of multidrug-resistant tuberculosis (MDR-TB) for the majority of patients. Given its long terminal

half-life and safety concerns, such as QTc-prolongation, re-introducing BDQ after multiple dose interruption is not intuitive and there are currently no existing guidelines. In this simulation-based study, we investigated different loading dose strategies for BDQ re-introduction, taking safety and efficacy into account. Multiple scenarios of time and length of interruption as well as BDQ re-introduction, including no loading dose, 1- and 2-week loading doses (200 mg and 400 mg once daily), were simulated from a previously published population pharmacokinetic (PK) model describing BDQ and its main metabolite M2 PK in patients with MDR-TB. The efficacy target was defined as 95.0% of the average BDQ concentration without dose interruption during standard treatment. Because M2 is the main driver for QTc-prolongation, the safety limit was set to be below the maximal average M2 metabolite concentration in a standard treatment. Simulations suggest that dose interruptions between treatment weeks 3 and 72 (interruption length: 1 to 6 weeks) require a 2-week loading dose of 200 mg once daily in the typical patient. If treatment was interrupted for longer than 8 weeks, a 2-week loading dose (400 mg once daily) was needed to reach the proposed efficacy target, slightly exceeding the safety limit. In conclusion, we here propose a strategy for BDQ re-introduction providing guidance to clinicians for safe and efficacious BDQ dosing.

DOI: 10.1002/psp4.12768
PMID: 35102712

50**. Moxifloxacin Pharmacokinetics, Cardiac Safety, and Dosing for the Treatment of Rifampicin-Resistant Tuberculosis in Children.**

Clin Infect Dis. 2022 Apr 28;74(8):1372-1381. doi: 10.1093/cid/ciab641.

Radtke KK(1), Hesseling AC(2), Winckler JL(2), Draper HR(2), Solans BP(1), Thee S(2)(3), Wiesner L(4), van der Laan LE(2), Fourie B(2), Nielsen J(5), Schaaf HS(2), Savic RM(1), Garcia-Prats AJ(2)(6).

BACKGROUND: Moxifloxacin is a recommended drug for rifampin-resistant tuberculosis (RR-TB) treatment, but there is limited pediatric pharmacokinetic and safety data, especially in young children. We characterize moxifloxacin population pharmacokinetics and QT interval prolongation and evaluate optimal dosing in children with RR-TB.
METHODS: Pharmacokinetic data were pooled from 2 observational studies in South African children with RR-TB routinely treated with oral moxifloxacin once daily. The population pharmacokinetics and Fridericia-corrected QT (QTcF)-interval

prolongation were characterized in NONMEM. Pharmacokinetic simulations were performed to predict expected exposure and optimal weight-banded dosing.
RESULTS: Eighty-five children contributed pharmacokinetic data (median [range] age of 4.6 [0.8-15] years); 16 (19%) were aged <2 years, and 8 (9%) were living with human immunodeficiency virus (HIV). The median (range) moxifloxacin dose on pharmacokinetic sampling days was 11 mg/kg (6.1 to 17). Apparent clearance was 6.95 L/h for a typical 16-kg child. Stunting and HIV increased apparent clearance. Crushed or suspended tablets had faster absorption. The median (range) maximum change in QTcF after moxifloxacin administration was 16.3 (-27.7 to 61.3) ms. No child had QTcF ≥500 ms. The concentration-QTcF relationship was nonlinear, with a maximum drug effect (Emax) of 8.80 ms (interindividual variability = 9.75 ms). Clofazimine use increased Emax by 3.3-fold. Model-based simulations of moxifloxacin pharmacokinetics predicted that current dosing recommendations are too low in children.
CONCLUSIONS: Moxifloxacin doses above 10-15 mg/kg are likely required in young children to match adult exposures but require further safety assessment, especially when coadministered with other QT-prolonging agents.

DOI: 10.1093/cid/ciab641
PMCID: PMC9049278
PMID: 34286843 [Indexed for MEDLINE]

51. Preventive treatment for MDR-TB exposure in households.

Int J Tuberc Lung Dis. 2022 May 1;26(5):466-467. doi: 10.5588/ijtld.22.0065.

Malik AA(1), Hussain H(2).

Comment on
Int J Tuberc Lung Dis. 2022 Feb 1;26(2):171-173.

DOI: 10.5588/ijtld.22.0065
PMID: 35505480 [Indexed for MEDLINE]

52. **Re-Evaluating the Merits of Decentralisation as a Core Strategy for Effective Delivery of Drug-Resistant Tuberculosis Care in Pakistan.**

Health Policy Plan. 2022 May 9:czac038. doi: 10.1093/heapol/czac038. Online ahead of print.

Khan U(1), Lotia-Farrukh I(1), Akhtar A(2), Khowaja SN(1), Khan S(3), Madhani F(2), Parekh A(1), Adnan S(2), Ahmed S(1), Chaudhry M(1), Hussain H(1), Habib A(4), Butt S(2), Siddiqui MR(3)(5), Ijaz R(2), Jamal S(2), Khan AB(2), Keshavjee S(6)(7), Khan AJ(1), Salahuddin N(2), Khan PY(1)(8).

Decentralised, person-centred models of care-delivery for drug-resistant tuberculosis (DR-TB) continue to be under-resourced in high burden TB countries. The implementation of such models - made increasingly urgent by the COVID-19 pandemic - are key to addressing gaps in DR-TB care. We abstracted data of RR/MDR-TB patients initiated on treatment at 11 facilities between 2010 and 2017 in Sindh and Balochistan provinces of Pakistan. We analysed trends in treatment outcomes relating to program expansion to peri-urban and rural areas and estimated driving distance from patient residence to treatment facility. Among the 5586 RR/MDR-TB patients in the analysis, overall treatment success decreased from 82% to 66% between 2010 and 2017, as the program expanded. The adjusted risk ratio for unfavourable outcomes was 1.013 (95% CI 1.005-1.021) for every 20 kilometres of driving distance. Our analysis suggests that expanding DR-TB care to centralised hubs added to increased unfavourable outcomes for people accessing care in peri-urban and rural districts. We propose that as enrolments increase, expanding DR-TB services close to or within affected communities is essential.

DOI: 10.1093/heapol/czac038
PMID: 35527232

53. **Intracellular Activity of Poly (DL-lactide-co-glycolide) Nanoparticles Encapsulated with Prothionamide, Pyrazinamide, Levofloxacin, Linezolid or Ethambutol on Multidrug-Resistant Mycobacterium Tuberculosis.**

Curr Drug Deliv. 2022 May 11. doi: 10.2174/1567201819666220511120215. Online ahead of print.

Jiang H(1), Li X(2), Xing Z(2), Niu Q(3), Xu J(1).

BACKGROUND: Multidrug-resistant Mycobacterium tuberculosis (MDR-TB) is a major cause of death amongst tuberculosis patients. Nanomedicine avoids some limitations of conventional drug treatment and increases therapeutic efficacy against bacterial infections. However, the effect of anti-TB drug nanoparticle (NP) compounds in anti-TB regimens against MDR-TB remains unclear. OBJECTIVE: The objective of this article is to prepare levofloxacin, linezolid,

ethambutol, prothionamide, and pyrazinamide encapsulated NPs and to evaluate their therapeutic efficacy against MDR-TB in macrophages.
METHODS: Drug-loaded PLGA NPs were prepared by the multiple emulsion method. The colocalization, intracellular release, and anti-TB activity of these NPs were investigated on cultured macrophages. The immune phenotype of the macrophages, including their mitochondrial membrane potential, reactive oxygen species (ROS), and nitric oxide (NO) production, was evaluated following treatment with NPs or free drug compounds.
RESULTS: All drug-loaded PLGA NPs were spherical in shape, 150 to 210 nm in size, and showed 14.22% to 43.51% encapsulation efficiencies and long-duration release. Drug-loaded PLGA NPs were mainly distributed in the cytoplasm of macrophages, showed high cellular compatibility, and maintained their concentration for at least 13 days. Compared with the free drug compounds, the number of colonies after exposure to PLGA NP compounds was significantly less. The enhanced antibacterial activity of the NP compounds may be due to the enhanced levels of ROS and NO and the increased early apoptosis stress within M. tuberculosis-infected macrophages additionally.
CONCLUSION: The application of PLGA NP compounds not only enhances drug efficacy but also induces innate bactericidal events in macrophages, confirming this as a promising approach for MDR-TB therapy.

DOI: 10.2174/1567201819666220511120215
PMID: 35546770

54. **Bone Penetration of Cycloserine in Osteoarticular Tuberculosis Patients of China.**

Antimicrob Agents Chemother. 2022 May 17;66(5):e0222421. doi: 10.1128/aac.02224-21. Epub 2022 Apr 11.

Zhang T(#)(1), Yu X(#)(1), Wen S(1), Xue Y(1), Xiao H(1), Ren R(1), Wang F(1), Dong L(1), Qin S(2), Huang H(1).

The cycloserine concentrations in plasma and bone that were collected during operations on 28 osteoarticular tuberculosis (TB) patients treated daily with a 500-mg cycloserine-containing regimen were determined. The median concentrations in plasma and bone were 16.29 μg/mL (interquartile range [IQR], 6.47 μg/mL) and 24.33 μg/g (IQR, 14.68 μg/g), respectively. The median bone/plasma penetration ratio was 0.76 (range, 0.33 to 1.98). Cycloserine could effectively penetrate bone and acquire concentrations comparable to those in plasma, which favors its usage in osteoarticular TB treatment.

DOI: 10.1128/aac.02224-21
PMCID: PMC9112879
PMID: 35400177 [Indexed for MEDLINE]

55**. Structure-activity relationship of 2-aminodibenzothiophene pharmacophore and the discovery of aminobenzothiophenes as potent inhibitors of Mycobacterium smegmatis.**

Bioorg Med Chem Lett. 2022 May 1;63:128650. doi: 10.1016/j.bmcl.2022.128650. Epub 2022 Mar 1.

Alelaiwi SH(1), Heindl JE(2), Sivaganesh V(2), Peethambaran B(2), McKee JR(3).

Tuberculosis (TB) is one of the deadliest infectious diseases worldwide and its current treatments have been complicated with the emergence of multi-drug resistant (MDR-TB) and extensively drug-resistant (XDR-TB) strains. Therefore, the discovery of new antitubercular agents is in need to overcome this problem. In our efforts to discover novel candidates for the treatment of tuberculosis, we describe in this work in vitro activityagainstM. smegmatis for a series of aminated benzo-fused heterocycles, particularly, dibenzothiophene to explore the structure-activity relationship of 2-aminodibenzothiophene 3aa. From these studies, three compounds 5-aminobenzothiophene 3ia, 6-aminobenzothiophene 3ma (MIC: 0.78 μg/mL) and 5-aminobenzofuran 3ja (MIC: 1.56 μg/mL) were identified as potent inhibitors of M. smegmatis with low cytotoxicity. These results suggested the significance of these compounds 3ia, 3ja and 3ma for the future development of candidate agents to treat tuberculosis.

DOI: 10.1016/j.bmcl.2022.128650
PMID: 35245664 [Indexed for MEDLINE]

56**. Detecting rifampin and isoniazid resistance in Mycobacterium tuberculosis direct from patient sputum using an automated integrated system.**

J Clin Tuberc Other Mycobact Dis. 2022 Feb 22;27:100304. doi: 10.1016/j.jctube.2022.100304. eCollection 2022 May.

Colman RE(1), Hagan C(1), Chiles P(1), Seifert M(1), Catanzaro DG(2), Kukhtin AV(3), Norville R(3), Hauns L(3), Bueno A(3), Holmberg RC(3), Cooney CG(3), Rodwell TC(1).

While there has been progress in detection of drug resistant tuberculosis

globally, WHO estimates only about half of the patients with bacteriologically confirmed tuberculosis were tested for rifampicin resistance over the past two years. To close this drug resistance diagnostic gap, an expansion of testing for rifampicin and isoniazid resistance is critically needed. The Akonni Biosystem Integrated System combines DNA extraction and a Lab-on-a-Film assembly (LFA) to perform rapid probe and PCR-based detection of resistance associated mutations to first-line anti-tuberculosis drugs. Using raw sputum samples from 25 tuberculosis patients at risk for drug resistance, we conducted a proof-of-concept study of the Integrated System with an MDR-TB assay. Performance of the Integrated System was compared to liquid Mycobacteria Growth Indicator Tube (MGIT) culture reference phenotypes using 2012 WHO endorsed critical concentrations for rifampicin and isoniazid. The overall percent agreement for rifampicin and isoniazid was 91.7% and 100% respectively, with agreement for rifampicin increasing to 95.7% after low-level resistance mutations in rpoB were excluded. The Integrated System, combining DNA extraction and LFA amplification, is a promising new tool for detection of both rifampicin and isoniazid using liquefied raw sputum.

DOI: 10.1016/j.jctube.2022.100304
PMCID: PMC8891689
PMID: 35252594

57**. Minimizing nephrotoxicity during multidrug-resistant tuberculosis treatment by the stepwise de-escalation of second-line injectables dosing intervals.**

Clin Microbiol Infect. 2022 May;28(5):752-754. doi: 10.1016/j.cmi.2022.01.023. Epub 2022 Feb 3.

Lin HC(1), Yu MC(2), Putri DU(1), Tsai YS(3), Chen JH(4), Lee CH(5).

DOI: 10.1016/j.cmi.2022.01.023
PMID: 35124260 [Indexed for MEDLINE]

58. **Delamanid Added to an Optimized Background Regimen in Children with Multidrug-Resistant Tuberculosis: Results of a Phase I/II Clinical Trial.**

Antimicrob Agents Chemother. 2022 May 17;66(5):e0214421. doi: 10.1128/aac.02144-21. Epub 2022 Apr 11.

Garcia-Prats AJ(1), Frias M(2), van der Laan L(1), De Leon A(3), Gler MT(2), Schaaf HS(1), Hesseling AC(1), Malikaarjun S(4), Hafkin J(4).

Delamanid has been demonstrated to be safe and effective for treatment of adult multidrug-resistant tuberculosis (MDR-TB) and has been approved by the European Commission for treatment of pediatric MDR-TB patients at least 10 kg in weight, making the drug no longer limited to adults. A 10-day phase I age deescalation study was conducted, followed by a 6-month phase II extension study, to assess the pharmacokinetics, safety, tolerability, and preliminary efficacy of delamanid when combined with optimized background regimen (OBR) in children (birth to 17 years) with MDR-TB. Delamanid administered at 100 mg twice-daily (BID), 50 mg BID, and 25 mg BID resulted in exposures in 12- to 17- (n = 7), 6- to 11- (n = 6), and 3- to 5-year-olds (n = 12), respectively, comparable with those in adults at the approved adult dosage (100 mg BID). Exposures in 0- to 2-year-olds (n = 12) following a weight-based dosing regimen (5 mg once daily [QD] to 10 mg BID) were lower than predicted from pharmacokinetic modeling of the older three age groups and below target exposures in adults. Overall, the safety profile of delamanid in children 0 to 17 years of age was similar to the adult profile. At 24 months after the first delamanid dose, 33/37 children (89.2%) had favorable treatment outcomes, as defined by the World Health Organization (15/37 [40.5%] cured and 18/37 [48.6%] completed treatment). A new pediatric delamanid formulation used in 0- to 2-year-olds and 3- to 5-year-olds was palatable per child/parent and nurse/investigator reports. Data from initial phase I/II studies inform our understanding of delamanid use in children and support its further assessment in the setting of pediatric MDR-TB. (This study has been registered at ClinicalTrials.gov under identifiers NCT01856634 [phase I trial] and NCT01859923 [phase II trial].).

DOI: 10.1128/aac.02144-21
PMCID: PMC9112969
PMID: 35404075 [Indexed for MEDLINE]

59. **Feasibility of a "Salvage Regimen" Using Home-based Intravenous Meropenem Therapy With a Delamanid/Bedaquilline Containing Regimen in the Management of MDR/XDR Pediatric Tuberculosis.**

Pediatr Infect Dis J. 2022 May 1;41(5):401-404. doi: 10.1097/INF.0000000000003486.

Shah I(1), Antony S(1), Jaiswal A(1), Bodhanwala M(2), Shah D(3), Tipre P(3), Salve J(4), Parmar M(4)(5), Sachdeva KS(6).

INTRODUCTION: The prevalence of multidrug resistant (MDR) tuberculosis (TB) with additional resistance to fluoroquinolones or second-line injectables (MDRFQ/SLI)/extensively drug-resistant TB (XDR-TB) in children is high in Mumbai. There are limited therapeutic options available in management of such children. Carbapenems, although approved for this indication, requires 2 to 3

daily injections, which are cumbersome. Bedaquilline (Bdq) and Delamanid (Dlm), the new antitubercular drugs still remain inaccessible to this subset of patients caused by conditional approvals. Hence, newer strategies to combat MDRFQ/SLI/XDR-TB needs to be explored.
OBJECTIVES: To study feasibility and interim outcomes of a "salvage regimen" using home-based carbapenem therapy through peripherally inserted central catheter as part of a longer (18-20 months) optimized background regimen including Dlm or Bdq or both in pediatric MDRFQ/SLI/XDR-TB patients who failed a standard MDR-TB regimen under the National Tuberculosis Elimination Programme in Mumbai, India.
DESIGN AND METHODS: Retrospective descriptive analysis study. National Tuberculosis Elimination Programme medical records of all MDRFQ/SLI/XDR-TB patients enrolled at the pediatric TB clinic at BJ Wadia Hospital for Children, Mumbai who were initiated on such "salvage regimen" during the period between April 2018 and December 2020 were retrospectively studied. Treatment outcomes and adverse events were described.
RESULTS: Of the 15 patients enrolled, mean age of the patient population was 12.53 ± 2.47 years and the female:male ratio was 13:2. Seven patients had XDR-TB while 8 patients had MDRFQ/SLI. Most common adverse event noted was dyselectrolytemia (3 patients). Catheter-related complications were reported in 5 patients and included catheter blockage, leak, and thrombosis. Sputum culture conversion was reported in all of the patients. One child mortality was reported and 2 patients were lost to follow up during study period.
CONCLUSIONS: Home-based meropenem therapy using peripherally inserted central catheter is feasible with few adverse effects. This can be a promising strategy in the management of MDRFQ/SLI/XDR-TB when an effective oral regimen cannot be otherwise constituted and needs to be explored further.

DOI: 10.1097/INF.0000000000003486
PMID: 35153288 [Indexed for MEDLINE]

60**. Post-tuberculosis lung disease: a comparison of Brazilian, Italian, and Mexican cohorts.**

J Bras Pneumol. 2022 May 13;48(2):e20210515. doi: 10.36416/1806-3756/e20210515. eCollection 2022.

Silva DR(1)(2), Freitas AA(1), Guimarães AR(2), D'Ambrosio L(3), Centis R(4), Muñoz-Torrico M(5), Visca D(6)(7), Migliori GB(4).

OBJECTIVE: To evaluate lung function in a cohort of patients with a history of pulmonary tuberculosis in Brazil, as well as to evaluate the decline in lung

function over time and compare it with that observed in similar cohorts in Mexico and Italy.
METHODS: The three cohorts were compared in terms of age, smoking status, pulmonary function test results, six-minute walk test results, and arterial blood gas results. In the Brazilian cohort, pulmonary function test results, six-minute walk test results, and arterial blood gas results right after the end of tuberculosis treatment were compared with those obtained at the end of the follow-up period.
RESULTS: The three cohorts were very different regarding pulmonary function test results. The most common ventilatory patterns in the Brazilian, Italian, and Mexican cohorts were an obstructive pattern, a mixed pattern, and a normal pattern (in 58 patients [50.9%], in 18 patients [41.9%], and in 26 patients [44.1%], respectively). Only 2 multidrug-resistant tuberculosis cases were included in the Brazilian cohort, whereas, in the Mexican cohort, 27 cases were included (45.8%). Mean PaO2 and mean SaO2 were lower in the Mexican cohort than in the Brazilian cohort ($p < 0.0001$ and $p < 0.002$ for PaO2 and SaO2, respectively). In the Brazilian cohort, almost all functional parameters deteriorated over time.
CONCLUSIONS: This study reinforces the importance of early and effective treatment of drug-susceptible tuberculosis patients, because multidrug-resistant tuberculosis increases lung damage. When patients complete their tuberculosis treatment, they should be evaluated as early as possible, and, if post-tuberculosis lung disease is diagnosed, they should be managed and offered pulmonary rehabilitation because there is evidence that it is effective in these patients.

DOI: 10.36416/1806-3756/e20210515
PMCID: PMC9064651
PMID: 35584466 [Indexed for MEDLINE]

61. **Rapid molecular tests for tuberculosis and tuberculosis drug resistance: a qualitative evidence synthesis of recipient and provider views.**

Cochrane Database Syst Rev. 2022 Apr 26;4(4):CD014877. doi: 10.1002/14651858.CD014877.pub2.

Engel N(1), Ochodo EA(2)(3), Karanja PW(4), Schmidt BM(5), Janssen R(1), Steingart KR(6), Oliver S(7)(8).

Update of
doi: 10.1002/14651858.CD014877.

BACKGROUND: Programmes that introduce rapid molecular tests for tuberculosis and tuberculosis drug resistance aim to bring tests closer to the community, and

thereby cut delay in diagnosis, ensure early treatment, and improve health outcomes, as well as overcome problems with poor laboratory infrastructure and inadequately trained personnel. Yet, diagnostic technologies only have an impact if they are put to use in a correct and timely manner. Views of the intended beneficiaries are important in uptake of diagnostics, and their effective use also depends on those implementing testing programmes, including providers, laboratory professionals, and staff in health ministries. Otherwise, there is a risk these technologies will not fit their intended use and setting, cannot be made to work and scale up, and are not used by, or not accessible to, those in need.

OBJECTIVES: To synthesize end-user and professional user perspectives and experiences with low-complexity nucleic acid amplification tests (NAATs) for detection of tuberculosis and tuberculosis drug resistance; and to identify implications for effective implementation and health equity.

SEARCH METHODS: We searched MEDLINE, Embase, CINAHL, PsycInfo and Science Citation Index Expanded databases for eligible studies from 1 January 2007 up to 20 October 2021. We limited all searches to 2007 onward because the development of Xpert MTB/RIF, the first rapid molecular test in this review, was completed in 2009.

SELECTION CRITERIA: We included studies that used qualitative methods for data collection and analysis, and were focused on perspectives and experiences of users and potential users of low-complexity NAATs to diagnose tuberculosis and drug-resistant tuberculosis. NAATs included Xpert MTB/RIF, Xpert MTB/RIF Ultra, Xpert MTB/XDR, and the Truenat assays. Users were people with presumptive or confirmed tuberculosis and drug-resistant tuberculosis (including multidrug-resistant (MDR-TB)) and their caregivers, healthcare providers, laboratory technicians and managers, and programme officers and staff; and were from any type of health facility and setting globally. MDR-TB is tuberculosis caused by resistance to at least rifampicin and isoniazid, the two most effective first-line drugs used to treat tuberculosis.

DATA COLLECTION AND ANALYSIS: We used a thematic analysis approach for data extraction and synthesis, and assessed confidence in the findings using GRADE CERQual approach. We developed a conceptual framework to illustrate how the findings relate.

MAIN RESULTS: We found 32 studies. All studies were conducted in low- and middle-income countries. Twenty-seven studies were conducted in high-tuberculosis burden countries and 21 studies in high-MDR-TB burden countries. Only one study was from an Eastern European country. While the studies covered a diverse use of low-complexity NAATs, in only a minority of studies was it used as the initial diagnostic test for all people with presumptive tuberculosis. We identified 18 review findings and grouped them into three overarching categories. Critical aspects users value People with tuberculosis valued reaching diagnostic closure with an accurate diagnosis, avoiding diagnostic delays, and keeping diagnostic-associated cost low.

Similarly, healthcare providers valued aspects of accuracy and the resulting confidence in low-complexity NAAT results, rapid turnaround times, and keeping cost to people seeking a diagnosis low. In addition, providers valued diversity of sample types (for example, gastric aspirate specimens and stool in children) and drug resistance information. Laboratory professionals appreciated the improved ease of use, ergonomics, and biosafety of low-complexity NAATs compared to sputum microscopy, and increased staff satisfaction. Challenges reported to realizing those values People with tuberculosis and healthcare workers were reluctant to test for tuberculosis (including MDR-TB) due to fears, stigma, or cost concerns. Thus, low-complexity NAAT testing is not implemented with sufficient support or discretion to overcome barriers that are common to other approaches to testing for tuberculosis. Delays were reported at many steps of the diagnostic pathway owing to poor sample quality; difficulties with transporting specimens; lack of sufficient resources; maintenance of low-complexity NAATs; increased workload; inefficient work and patient flows; over-reliance on low-complexity NAAT results in lieu of clinical judgement; and lack of data-driven and inclusive implementation processes. These challenges were reported to lead to underutilization. Concerns for access and equity The reported concerns included sustainable funding and maintenance and equitable use of resources to access low-complexity NAATs, as well as conflicts of interest between donors and people implementing the tests. Also, lengthy diagnostic delays, underutilization of low-complexity NAATs, lack of tuberculosis diagnostic facilities in the community, and too many eligibility restrictions hampered access to prompt and accurate testing and treatment. This was particularly the case for vulnerable groups, such as children, people with MDR-TB, or people with limited ability to pay. We had high confidence in most of our findings.

AUTHORS' CONCLUSIONS: Low-complexity diagnostics have been presented as a solution to overcome deficiencies in laboratory infrastructure and lack of skilled professionals. This review indicates this is misleading. The lack of infrastructure and human resources undermine the added value new diagnostics of low complexity have for recipients and providers. We had high confidence in the evidence contributing to these review findings. Implementation of new diagnostic technologies, like those considered in this review, will need to tackle the challenges identified in this review including weak infrastructure and systems, and insufficient data on ground level realities prior and during implementation, as well as problems of conflicts of interest in order to ensure equitable use of resources.

DOI: 10.1002/14651858.CD014877.pub2
PMCID: PMC9038447

PMID: 35470432 [Indexed for MEDLINE]

62**. Identification of nitrofuranylchalcone tethered benzoxazole-2-amines as potent inhibitors of drug resistant Mycobacterium tuberculosis demonstrating bactericidal efficacy.**

Bioorg Med Chem. 2022 Jun 15;64:116777. doi: 10.1016/j.bmc.2022.116777. Epub 2022 Apr 23.

Kumar Sahoo S(1), Maddipatla S(1), Nageswara Rao Gajula S(2), Naiyaz Ahmad M(3), Kaul G(3), Nanduri S(1), Sonti R(4), Dasgupta A(5), Chopra S(6), Madhavi Yaddanapudi V(7).

Ever increasing drug resistance has become an impeding threat that continues to hamper effective tackling of otherwise treatable tuberculosis (TB). Such dismal situation necessitates identification and exploration of multitarget acting newer chemotypes with bactericidal efficacy as a priority, that could efficiently hinder uncontrolled spread of TB. In this context, herein we present design, synthesis and bio-evaluation of chalcone tethered bezoxazole-2-amines as promising anti-TB chemotypes. Preliminary screening of 24 compounds revealed initial hits 3,4,5-trimethoxyphenyl and 5-nitrofuran-2-yl derivative exhibiting selective inhibition of Mycobacterium tuberculosis (Mtb) H37Rv. Further, structural optimization of hit compounds generated 12 analogues, amongst which 5-nitrofuran-2-yl derivatives displayed potent inhibition of not only drug-susceptible (DS) Mtb but also clinical isolates of drug-resistant (DR) Mtb strains equipotently. Moreover, cell viability test against Vero cells found these compounds with favourable selectivity. Time kill analysis led to the identification of the lead compound (E)-1-(4-((5-chlorobenzo[d]oxazol-2-yl)amino)phenyl)-3-(5-nitrofuran-2-yl)prop-2-en-1-one, that demonstrated bactericidal killing of Mtb bacilli. Together with acceptable microsomal stability, the lead compound of the series manifested all desirable traits of a promising antitubercular agent.

DOI: 10.1016/j.bmc.2022.116777
PMID: 35487101 [Indexed for MEDLINE]

63**. Predictors of loss to follow-up among adult tuberculosis patients in Southern Ethiopia: a retrospective follow-up study.**

BMC Public Health. 2022 May 14;22(1):976. doi: 10.1186/s12889-022-13390-8.

Watumo D(#)(1), Mengesha MM(#)(2), Gobena T(3), Gebremichael MA(4), Jerene D(5).

BACKGROUND: Loss to follow-up (LTFU) from tuberculosis (TB) treatment and care is a major public health problem as patients can be infectious and also may develop a multi-drug resistant TB (MDR-TB). The study aimed to assess whether LTFU differs by the distance TB patients travelled to receive care from the nearest health facility.
METHODS: A total of 402 patient cards of TB patients who received care were reviewed from March 1-30, 2020. The Kaplan-Meir curve with the Log-rank test was used to compare differences in LTFU by the distance travelled to reach to the nearest health facility for TB care. The Cox proportional hazard regression model was used to identify predictors. All statistical tests are declared significant at a p-value< 0.05.
RESULTS: A total of 37 patients were LTFU with the incidence rate of 11.26 per 1000 person-months of observations (PMOs) (95% CI: 8.15-15.53). The incidence rate ratio was 12.19 (95% CI: 5.01-35.73) among the groups compared (those who travelled 10 km or more versus those who travelled less than 10 km).
Age ≥ 45 years (aHR = 7.71, 95% CI: 1.72, 34.50), educational status (primary schooling, aHR = 3.54, 95% CI: 1.49, 8.40; secondary schooling, aHR = 2.75, 95% CI: 1.08, 7.03), lack of family support (aHR = 2.80, 95% CI: 1.27, 6.19), nutritional support (aHR = 3.40, 95% CI:1.68, 6.89), ≥ 10 km distance to travel to a health facility (aHR = 6.06, 95% CI: 2.33, 15.81) had significantly predicted LTFU from TB treatment and care.
CONCLUSIONS: LTFU from adult TB care and treatment was 12 times higher among those who travelled ≥10 km to reach a health facility compared to those who travelled less. To retain adult TB patients in care and ensure appropriate treatment, health professionals and other stakeholders should give due attention to the factors that drive LTFU. We suggest identifying concerns of older patients at admission and those who travel long distance and establish social support platforms that could help people to complete TB treatment.

DOI: 10.1186/s12889-022-13390-8
PMCID: PMC9107690
PMID: 35568853 [Indexed for MEDLINE]

64**. Frequent Suboptimal Thermocycler Ramp Rate Usage Negatively Impacts GenoType MTBDRsl VER 2.0 Performance for Second-Line Drug-Resistant Tuberculosis Diagnosis.**

J Mol Diagn. 2022 May;24(5):494-502. doi: 10.1016/j.jmoldx.2022.01.003. Epub 2022 Jan 31.

Derendinger B(1), de Vos M(1), Pillay S(1), Venter R(1), Metcalfe J(2),

Ghebrekristos Y(3), Minnies S(1), Dolby T(4), Beylis N(4), Warren R(1), Theron G(5).

Strengthening second-line drug-resistant tuberculosis (TB) detection is a priority. GenoType MTBDRplus VER 2.0 performance is reduced with non-recommended ramp rate usage (temperature change speed between PCR cycles); however, ramp rate's effect on GenoType MTBDRsl VER 2.0 (MTBDRsl) performance, is unknown. Fifty-two Xpert MTB/RIF Ultra-positive rifampicin-resistant smear-negative sputa and a Mycobacterium tuberculosis dilution series were tested at a manufacturer-recommended (2.2°C/second) or suboptimal (4.0°C/second) ramp rate. M. tuberculosis-complex-DNA positivity, indeterminates, fluoroquinolone- and second-line injectable-resistance accuracy, banding differences, and, separately, inter-reader variability were assessed. Five (39%) of 13 re-surveyed laboratories did not use the manufacturer-recommended ramp rate. On sputum, 2.2°C/second improved indeterminates versus 4.0°C/second (0 of 52 versus 7 of 51; P = 0.006), incorrect drug-class diagnostic calls (0 of 104 versus 6 of 102; P = 0.013), and incorrect banding calls (0 of 1300 versus 54 of 1275; P < 0.001). Similarly, 2.2°C/second improved valid results [(52 of 52 versus 41 of 51; +21% (P = 0.001)] and banding call inter-reader variability [34 of 1300 (3%) versus 52 of 1300 (4%); P = 0.030]. At the suboptimal ramp rate, false-resistance and false-susceptible calls resulted from wild-type band absence rather than mutant band appearance, resulting in misclassification of moxifloxacin resistance level from high-to-low. Suboptimal ramp rate contributes to poor MTBDRsl performance. Laboratories must ensure that the manufacturer-recommended ramp rate is used.

DOI: 10.1016/j.jmoldx.2022.01.003
PMID: 35108607 [Indexed for MEDLINE]

65**. In vitro antimycobacterial activity of medicinal plants Lantana camara, Cryptolepis sanguinolenta, and Zanthoxylum leprieurii.**

J Clin Tuberc Other Mycobact Dis. 2022 Mar 3;27:100307. doi: 10.1016/j.jctube.2022.100307. eCollection 2022 May.

Tuyiringire N(1)(2), Taremwa Mugisha I(3), Tusubira D(4), Munyampundu JP(5), Mambo Muvunyi C(6), Vander Heyden Y(7).

BACKGROUND: Imperative need exists to search for new anti-TB drugs that are safer, and more effective against drug-resistant strains. Medicinal plants have been the source of active ingredients for drug development. However, the slow

growth and biosafety level requirements of M. tuberculosis culture are considerable challenges. M. smegmatis can be used as a surrogate for M. tuberculosis. In the current study, preliminary phytochemical screening and antimycobacterial activity evaluation of crude methanolic extracts of medicinal plants against M. smegmatis, and two M. tuberculosis strains, were conducted.
MATERIALS AND METHODS: Crude methanolic extracts, obtained from the leaves of L. camara, roots of C. sanguinolenta, and stem barks of Z. leprieurii, were tested for antimycobacterial activity against M. smegmatis (mc2155), pan-sensitive (H37Rv), and rifampicin-resistant (TMC-331) M. tuberculosis, using visual Resazurin Microtiter Assay (REMA) on 96 well plates. Preliminary qualitative phytochemical screening tests were performed using standard chemical methods.
RESULTS: The three methanolic extracts inhibited mycobacterial growth in vitro. They were more active against rifampicin-resistant strain with MICs of 176, 97, and 45 µg/mL for L. camara, C. sanguinolenta, and Z. leprieurii extracts, respectively. The lowest activity was observed against M. smegmatis with MICs of 574, 325, and 520 µg/mL, respectively. Against H37Rv, activity was intermediate to those of TMC-331 and mc2155. However, L. camara extract showed the same activity against H37Rv and M. smegmatis. Preliminary phytochemical analysis revealed alkaloids, flavonoids, phenolic compounds, saponins, tannins, and terpenoids.
CONCLUSIONS: Leaves of L. camara, roots of C. sanguinolenta, and stem barks of Z. leprieurii exhibit antimycobacterial activity against M. smegmatis, pan-sensitive, and rifampicin-resistant M. tuberculosis. This offers the possibilities for novel therapeutic opportunities against TB including multidrug-resistant TB. Further investigations on safety and mechanisms of action are required. These studies could be done using M. smegmatis as a surrogate for the highly pathogenic M. tuberculosis.

DOI: 10.1016/j.jctube.2022.100307
PMCID: PMC8904236
PMID: 35284659

66. **Frequency of CD4(+) regulatory T cells and modulation of CD4(+)T lymphocyte activation in pleural tuberculoma.**

Tuberculosis (Edinb). 2022 May 2;134:102210. doi: 10.1016/j.tube.2022.102210. Online ahead of print.

Gao W(1), Yang N(2), Ji S(3), Zeng Y(4).

BACKGROUND: The expression of regulatory T cells (Tregs) is elevated in patients with active tuberculosis (TB) or multidrug-resistant TB. However, it remains

uncertain whether Tregs mediate immune suppression in pleural tuberculoma (PTM).
METHODS: Peripheral venous blood and clinical data were collected from 56 PTM patients and 50 healthy volunteers. The expression of CD38 and HLA-DR expression in T cell subsets and Tregs was determined by flow cytometry.
RESULTS: PTM patients had significantly more Tregs than the matched healthy controls. The expression of CD4+T cells normalized after treatment. Although the median proportions of CD3+T, CD4+T, and CD8+T lymphocytes did not differ significantly between PTM patients and healthy controls, the CD4/CD8 ratio was higher in PTM patients. Moreover, the proportion of CD4+T lymphocytes expressing activation markers, including HLA-DR and CD38, was higher in PTM patients than healthy controls. Treg expression was positively associated with the level of CD4+T lymphocyte activation.
CONCLUSIONS: The increased expression of Tregs seen in PTM patients, and subsequent decrease after treatment, indicate that Tregs play an important role in the immune reactivity of PTM.

DOI: 10.1016/j.tube.2022.102210
PMID: 35526509

67**. Close Related Drug-Resistance Beijing Isolates of Mycobacterium tuberculosis Reveal a Different Transcriptomic Signature in a Murine Disease Progression Model.**

Int J Mol Sci. 2022 May 5;23(9):5157. doi: 10.3390/ijms23095157.

Cerezo-Cortés MI(1), Rodríguez-Castillo JG(1), Mata-Espinosa DA(2), Bini EI(2), Barrios-Payan J(2), Zatarain-Barrón ZL(2), Anzola JM(3)(4), Cornejo-Granados F(5), Ochoa-Leyva A(5), Del Portillo P(3), Murcia MI(1), Hernández-Pando R(2).

Mycobacterium tuberculosis (MTB) lineage 2/Beijing is associated with high virulence and drug resistance worldwide. In Colombia, the Beijing genotype has circulated since 1997, predominantly on the pacific coast, with the Beijing-Like SIT-190 being more prevalent. This genotype conforms to a drug-resistant cluster and shows a fatal outcome in patients. To better understand virulence determinants, we performed a transcriptomic analysis with a Beijing-Like SIT-190 isolate (BL-323), and Beijing-Classic SIT-1 isolate (BC-391) in progressive tuberculosis (TB) murine model. Bacterial RNA was extracted from mice lungs on days 3, 14, 28, and 60. On average, 0.6% of the total reads mapped against MTB genomes and of those, 90% against coding genes. The strains were independently associated as determined by hierarchical cluster and multidimensional scaling analysis. Gene ontology showed that in strain BL-323 enriched functions were related to host immune response and hypoxia, while proteolysis and protein

folding were enriched in the BC-391 strain. Altogether, our results suggested a differential bacterial transcriptional program when evaluating these two closely related strains. The data presented here could potentially impact the control of this emerging, highly virulent, and drug-resistant genotype.

DOI: 10.3390/ijms23095157
PMCID: PMC9100210
PMID: 35563545 [Indexed for MEDLINE]

68. **MIC of cycloserine against Mycobacterium tuberculosis using the MGIT 960 system and a proposed critical concentration.**

Int J Infect Dis. 2022 May 13:S1201-9712(22)00293-4. doi: 10.1016/j.ijid.2022.05.030. Online ahead of print.

Wu X(1), Shang Y(1), Ren W(1), Wang W(1), Wang Y(2), Xue Z(1), Li S(3), Pang Y(4).

OBJECTIVE: We aimed to determine the breakpoint of cycloserine (CS) susceptibility in MGIT, and to describe the molecular characteristics of CS-resistant Mycobacterium tuberculosis (MTB) isolates.
METHODS: 124 MTB isolates were recruited in our analysis. Minimum inhibitory concentration (MIC) was determined using MGIT system. The mutations of MTB isolates within alr, ddl, ald, and cycA potentially conferring CS resistance were analyzed by the whole-genome sequencing.
RESULTS: In vitro DST of isolates with doubling concentrations of CS revealed that the modal MIC values was 4 mg/L for MGIT, accounting for 35.5% (44/124) of isolates tested. Seven isolates harbored mutations conferring CS resistance, consisting of 5 with alr mutations and 2 with ald mutations. Based on the minimum inhibitory concentration distributions of wild-type and resistotype populations, we proposed a tentative epidemiological cut-off value (TECOFF) of 16 mg/L. The proportion of CS-resistance in extensively drug-resistant tuberculosis was significantly higher than that of multidrug-resistant tuberculosis.
CONCLUSION: In conclusion, we propose critical concentration for MGIT 960 to properly diagnose CS-resistant MTB and demonstrates that mutations in alr and ald gene are the major mechanism conferring CS resistance in clinical isolates.

DOI: 10.1016/j.ijid.2022.05.030
PMID: 35577251

69**. Molecular dynamic assisted investigation on impact of mutations in deazaflavin**

dependent nitroreductase against pretomanid: a computational study.

J Biomol Struct Dyn. 2022 May 14:1-23. doi: 10.1080/07391102.2022.2069156.
Online ahead of print.

Singh R(1), Shaheer M(1), Sobhia ME(1).

In the past decade, TB drugs belonging to the nitroimidazole class, pretomanid and delamanid, have been authorised to treat MDR-TB and XDR-TB. With a novel inhibition mechanism and a reduction in the span of treatment, it is now being administered in various combinations. This approach is not the ultimate remedy since the target protein Deazaflavin dependent nitroreductase (Ddn) has a high mutation frequency, and already pretomanid resistant clinical isolates are reported in various studies. Ddn is essential for M.tuberculosis to emerge from hypoxia, and point mutations in critical residues confer resistance to Nitro-imidazoles. Among the pool of available mutants, we have selected seven mutants viz DdnL49P, DdnY65S, DdnS78Y, DdnK79Q, DdnW88R, DdnY133C, and DdnY136S, all of which exhibited resistance to pretomanid. To address this issue, through computational study primarily by MD simulation, we attempted to elucidate these point mutations' impact and investigate the resistance mechanism. Hence, the DdnWT and mutant (MT) complexes were subjected to all-atom molecular dynamics (MD) simulations for 100 ns. Interestingly, we observed the escalation of the distance between cofactor and ligand in some mutants, along with a significant change in ligand conformation relative to the DdnWT. Moreover, we confirmed that mutations rendered ligand instability and were ejected from the binding pocket as a result. In conclusion, the results obtained provide a new structural insight and vital clues for designing novel inhibitors to combat nitroimidazole resistanceCommunicated by Ramaswamy H. Sarma.

DOI: 10.1080/07391102.2022.2069156
PMID: 35574601

70**. Comprehensive genomic analysis of Mycobacterium tuberculosis reveals limited impact of high-fitness genotypes on MDR-TB transmission.**

J Infect. 2022 May 16:S0163-4453(22)00293-6. doi: 10.1016/j.jinf.2022.05.012.
Online ahead of print.

Chen Y(1), Liu Q(2), Takiff HE(3), Gao Q(4).

OBJECTIVES: Environmental and host-related factors that contribute to the transmission of multidrug-resistant tuberculosis (MDR-TB) have become an increasing concern, but the impact of bacterial genetic factors associated with bacterial fitness on MDR-TB transmission is poorly understood. Here, we present

a global view of the correlation between common fitness-related genotypes and MDR-TB transmission by analyzing a representative number of MDR-TB isolates.
METHODS: We assembled a global whole genome sequencing (WGS) dataset of MDR-TB strains collected through retrospective cohorts or population-based approaches using public databases and literature curation. WGS-based clusters were defined as groups of strains with genomic difference of ≤ 5 SNPs.
RESULTS: We curated high-quality WGS data of 4696 MDR-TB isolates from 17 countries with a mean clustering rate of 48% (range 0-100%). Correlational analysis showed that increased risk of MDR-TB strain clustering was not associated with compensatory mutations (OR 1.07, 95% CI 0.72-1.59), low-fitness cost drug-resistant mutations (katG S315T: OR 1.42, 95% CI 0.82-2.47; rpoB S450L: OR 1.26, 95% CI 0.87-1.83) or Lineage 2 (OR 1.50, 95% CI 0.95-2.39).
CONCLUSIONS: The factors most commonly thought to increase bacterial fitness were not significantly associated with increased MDR-TB transmission, and thus do not appear to be major contributors to the current epidemic of MDR-TB.

DOI: 10.1016/j.jinf.2022.05.012
PMID: 35588941

71**. Uganda Public Health Fellowship Program's Contributions to the National HIV and TB Programs, 2015-2020.**

Glob Health Sci Pract. 2022 Apr 29;10(2):e2100574. doi: 10.9745/GHSP-D-21-00574. Print 2022 Apr 28.

Ario AR(1)(2)(3), Bulage L(2)(3)(4), Wibabara Y(2), Muwereza P(2), Eurien D(2), Kabwama SN(2)(5), Kwesiga B(2)(3), Kadobera D(2)(3), Turyahabwe S(6)(7), Musinguzi JB(6)(8), Wanyenze RK(5), Nasirumbi PM(9), Lukoye D(9), Harris JR(9), Mills LA(10), Nelson LJ(10).

Despite remarkable progress in controlling HIV and TB, Uganda is one of the 30 high-burden TB/HIV countries. Approximately 53,000 Ugandans had a new HIV diagnosis in 2019, and approximately 88,000 Ugandans had a TB diagnosis in 2020. Fellows in the Uganda Public Health Fellowship Program (UPHFP) work directly with the Ministry of Health AIDS and TB Control Programs, the U.S. Centers for Disease Control and Prevention, UPHFP supervisors, and implementing partners to investigate and evaluate HIV-related and TB-related issues. These activities have contributed to the Uganda HIV and TB programs. UPHFP fellows complete projects in 7 competency domains, including outbreak investigations, surveillance evaluations, and data quality improvement. Priority HIV/AIDS/TB information gaps/topics are identified in consultation with key stakeholders, and fellows complete projects to guide program improvements and policy

decisions. During 2015-2020, UPHFP fellows implemented 127 HIV and TB projects covering key program areas in AIDS and TB control programs, including care and treatment (16 projects), TB/HIV (18), prevention of mother-to-child HIV transmission (24), key and priority populations (9), pre-exposure and post-exposure prophylaxis (7), adolescent girls and young women (6), service delivery (13), and diagnosis of TB including drug-resistant TB and TB in high-risk groups (32). These projects have helped improve retention, quality of care, and treatment outcomes for people living with HIV, HIV and TB coinfected patients, and TB patients. They have also contributed to the decrease in pediatric TB and infant HIV positivity rates and improved service delivery for key populations. UPHFP results were disseminated to relevant stakeholders such as government departments, implementing partners, districts, and the general community and guided decision making. UPHFP has significantly improved HIV and TB control in Uganda. Other countries with similar programs could benefit from this approach and utilize program fellows to support HIV and TB control.

DOI: 10.9745/GHSP-D-21-00574
PMCID: PMC9053155
PMID: 35487554 [Indexed for MEDLINE]

72**. Treatment outcomes 24 months after initiating short, all-oral bedaquiline-containing or injectable-containing rifampicin-resistant tuberculosis treatment regimens in South Africa: a retrospective cohort study.**

Lancet Infect Dis. 2022 May 2:S1473-3099(21)00811-2. doi: 10.1016/S1473-3099(21)00811-2. Online ahead of print.

Ndjeka N(1), Campbell JR(2), Meintjes G(3), Maartens G(3), Schaaf HS(4), Hughes J(4), Padanilam X(5), Reuter A(6), Romero R(7), Ismail F(8), Enwerem M(9), Ferreira H(10), Conradie F(11), Naidoo K(12), Menzies D(2).

BACKGROUND: There is a need for short and safe all-oral treatment of rifampicin-resistant tuberculosis. We compared outcomes up to 24 months after treatment initiation for patients with rifampicin-resistant tuberculosis in South Africa treated with a short, all-oral bedaquiline-containing regimen (bedaquiline group), or a short, injectable-containing regimen (injectable group).
METHODS: Patients with rifampicin-resistant tuberculosis, aged 18 years or older, eligible for a short regimen starting treatment between Jan 1 and Dec 31, 2017, with a bedaquiline-containing or WHO recommended injectable-containing treatment regimen of 9-12 months, registered in the drug-resistant tuberculosis database (EDRWeb), and with known age, sex, HIV status, and national

identification number were eligible for study inclusion; patients receiving linezolid, carbapenems, terizidone or cycloserine, delamanid, or para-aminosalicylic acid were excluded. Bedaquiline was given at a dose of 400 mg once daily for two weeks followed by 200 mg three times a week for 22 weeks. To compare regimens, patients were exactly matched on HIV and ART status, previous tuberculosis treatment history, and baseline acid-fast bacilli smear and culture result, while propensity score matched on age, sex, province of treatment, and isoniazid-susceptibility status. We did binomial linear regression to estimate adjusted risk differences (aRD) and 95% CIs for 24-month outcomes, which included: treatment success (ie, cure or treatment completion without evidence of recurrence) versus all other outcomes, survival versus death, disease free survival versus survival with treatment failure or recurrence, and loss to follow-up versus all other outcomes.
FINDINGS: Overall, 1387 (14%) of 10152 patients with rifampicin-resistant tuberculosis treated during 2017 met inclusion criteria; 688 in the bedaquiline group and 699 in the injectable group. Four patients (1%) had treatment failure or recurrence, 44 (6%) were lost to follow-up, and 162 (24%) died in the bedaquiline group, compared with 17 (2%), 87 (12%), and 199 (28%), respectively, in the injectable group. In adjusted analyses, treatment success was 14% (95% CI 8-20) higher in the bedaquiline group than in the injectable group (70% vs 57%); loss to follow-up was 4% (1-8) lower in the bedaquiline group (6% vs 12%); and disease-free survival was 2% (0-5) higher in the bedaquiline group (99% vs 97%). The bedaquiline group had 8% (4-11) lower risk of mortality during treatment (17·0% vs 22·4%), but there was no difference in mortality post-treatment.
INTERPRETATION: Patients in the bedaquiline group experienced significantly higher rates of treatment success at 24 months. This finding supports the use of short bedaquiline-containing regimens in eligible patients.
FUNDING: WHO Global TB Programme.
TRANSLATION: For the French translation of the abstract see Supplementary Materials section.

DOI: 10.1016/S1473-3099(21)00811-2
PMID: 35512718

73. Rapid molecular diagnostics to detect resistance to second-line anti-TB drugs.

Int J Tuberc Lung Dis. 2022 May 1;26(5):385-387. doi: 10.5588/ijtld.22.0121.

Kritski AL(1), Viveiros M(2), Carvalho ACC(3).

Comment on
Int J Tuberc Lung Dis. 2022 May 1;26(5):426-432.

DOI: 10.5588/ijtld.22.0121
PMID: 35505483 [Indexed for MEDLINE]

74. **Intra-host genetic population diversity: Role in emergence and persistence of drug resistance among Mycobacterium tuberculosis complex minor variants.**

Infect Genet Evol. 2022 Apr 27;101:105288. doi: 10.1016/j.meegid.2022.105288. Online ahead of print.

Vázquez-Chacón CA(1), de Jesús Rodríguez-Gaxiola F(2), Sánchez-Flores A(3), Montaño S(2), Bello-Rios C(4), Fonseca-Coronado S(5), López-Carrera CF(6), Martínez-Guarneros A(7), Parra-Unda R(2), García-Magallanes N(8), Arámbula-Meraz E(2), Escobar-Gutiérrez A(7), Cruz-Rivera M(9), López-Durán PA(10).

Drug resistant tuberculosis (DR-TB) is an important public health issue in different parts of the world. Mycobacterium tuberculosis complex variants (MTBC vars) preferentially infect certain hosts, limiting their distribution to different ecosystems. However, MTBC vars can infect other hosts beyond their preferred target potentially contributing to persistence of drug resistance (DR) in other niches. Here, we performed a comprehensive intra-host genetic analysis for the identification of DR-related mutations among all MTBC minor vars whole genome sequences (8,095 strains) publicly available worldwide. High confidence drug-resistance mutations in katG (isoniazid), rpsL (streptomycin), pncA (pyrazinamide), rpoB (rifampicin) and gyrA (fluoroquinolones) genes were identified among intrahost minor sub-populations in 197 different strains (2.43%) belonging to vars africanum, bovis, caprae, microti, orygis and pinnipedii. In addition, a three-dimensional structure modeling analysis to assess the role of novel mutations was also performed. Our findings highlight the importance of detecting discrete intra-host populations carrying DR mutations.

DOI: 10.1016/j.meegid.2022.105288
PMID: 35489699

75**. 24 loci MIRU-VNTR analysis and pattern of drug resistance in pre-extensively drug resistant pulmonary tuberculosis in Bangladesh.**

Infect Genet Evol. 2022 May 17:105304. doi: 10.1016/j.meegid.2022.105304. Online ahead of print.

Monir BB(1), Sultana SS(2), Tarafder S(3).

Phylogenetic diversity and distinct phylogeographic distribution of Mycobacterium tuberculosis (MTB) contribute to regional differences in drug resistance. The emergence of pre-extensively drug resistant tuberculosis (Pre-XDR-TB) becomes obstacles to achieve End TB strategy in Bangladesh. This cross-sectional study was conducted to identify the strains of different lineages of MTB, their variations of distribution among Pre-XDR-TB cases and to observe the linkage of particular strains of MTB with drug resistance. A total of 33 Pre-XDR-TB isolates were enrolled in this study. All isolates were confirmed as MTB by MPT 64 antigen detection and genotyped by 24 loci Mycobacterial Interspersed Repetitive Unit-Variable Number of Tandem Repeats (MIRU-VNTR) analysis. Drug resistance was detected by second line Line probe assay (LPA). Beijing was the predominant strain 16 (48.48%), followed by Delhi/CAS 5(15.15%), LAM 4 (12.12%) and Harlem 3(9.10%), EAI 2(6.06%), Cameroon 2(6.06%) and NEW-1 1(3.03%). There were 31 different genotypes consisting of 2 clusters and 29 singletons. All the clustered strains were belonged to Beijing lineage. Recent transmission occurred manly by Beijing strains, showed low transmission rate (12.1%). Of 33 isolates 30(90.90%) were Fluoroquinolones resistant, the mutations involved was Asp94Gly in gyr A MUT 3C gene 13(39.39%) in quinolone resistance determining region (QRDR) followed by 11 (33.33%) in gyr A MUT 1. Three (9.10%) isolates showed resistant to injectable 2nd line drugs and all mutation occurs in G1484T of rrs MUT 2. Beijing lineage was predominant in treatment failure and relapse cases. Levofloxacin was resistant to all Pre-XDR-TB cases, but moxifloxacin showed low level resistance. QUB 26 was the most discriminatory locus (0.85) among 24 loci whereas MIRU 2 was the least (0.03). 24 loci MIRU-VNTR analysis shows high discriminatory index (0.71), found to be powerful tool for genotyping of Pre-XDR-TB, which is the first study in Bangladesh that enhanced the current TB control policy.

DOI: 10.1016/j.meegid.2022.105304
PMID: 35595025

76. **Use of Whole-Genome Sequencing to Predict Mycobacterium tuberculosis Complex Drug Resistance from Early Positive Liquid Cultures.**

Microbiol Spectr. 2022 Apr 27;10(2):e0251621. doi: 10.1128/spectrum.02516-21. Epub 2022 Mar 21.

Wu X(#)(1), Tan G(#)(2), Sha W(3), Liu H(4), Yang J(1), Guo Y(1), Shen X(5), Wu Z(5), Shen H(3), Yu F(1).

Our objective was to evaluate the performance of whole-genome sequencing (WGS) from early positive liquid cultures for predicting Mycobacterium tuberculosis complex (MTBC) drug resistance. Clinical isolates were obtained from tuberculosis patients at Shanghai Pulmonary Hospital (SPH). Antimicrobial susceptibility testing (AST) was performed, and WGS from early Bactec mycobacterial growth indicator tube (MGIT) 960-positive liquid cultures was performed to predict the drug resistance using the TB-Profiler informatics platform. A total of 182 clinical isolates were enrolled in this study. Using phenotypic AST as the gold standard, the overall sensitivity and specificity for WGS were, respectively, 97.1% (89.8 to 99.6%) and 90.4% (83.4 to 95.1%) for rifampin, 91.0% (82.4 to 96.3%) and 95.2% (89.1 to 98.4%) for isoniazid, 100.0% (89.4 to 100.0%) and 87.3% (80.8 to 92.1%) for ethambutol, 96.6% (88.3 to 99.6%) and 61.8% (52.6 to 70.4%) for streptomycin, 86.8% (71.9 to 95.6%) and 95.8% (91.2 to 98.5%) for moxifloxacin, 86.5% (71.2 to 91.5%) and 95.2% (90.3 to 98.0%) for ofloxacin, 100.0% (54.1 to 100.0%) and 67.6% (60.2 to 74.5%) for amikacin, 100.0% (63.1 to 100.0%) and 67.2% (59.7 to 74.2%) for kanamycin, 62.5% (24.5 to 91.5%) and 88.5% (82.8 to 92.8%) for ethionamide, 33.3% (4.3 to 77.7%) and 98.3% (95.1 to 99.7%) for para-aminosalicylic acid, and 0.0% (0.0 to 12.3%) and 100.0% (97.6 to 100.0%) for cycloserine. The concordances of WGS-based AST and phenotypic AST were as follows: rifampin (92.9%), isoniazid (93.4%), ethambutol (89.6%), streptomycin (73.1%), moxifloxacin (94.0%), ofloxacin (93.4%), amikacin (68.7%), kanamycin (68.7%), ethionamide (87.4%), para-aminosalicylic acid (96.2%) and cycloserine (84.6%). We conclude that WGS could be a promising approach to predict MTBC resistance from early positive liquid cultures. IMPORTANCE In this study, we used whole-genome sequencing (WGS) from early positive liquid (MGIT) cultures instead of solid cultures to predict drug resistance of 182 Mycobacterium tuberculosis complex (MTBC) clinical isolates to predict drug resistance using the TB-Profiler informatics platform. Our study indicates that WGS may be a promising method for predicting MTBC resistance using early positive liquid cultures.

DOI: 10.1128/spectrum.02516-21
PMCID: PMC9045259
PMID: 35311541 [Indexed for MEDLINE]

77. **atpE Mutation in Mycobacterium tuberculosis Not Always Predictive of Bedaquiline Treatment Failure.**

Emerg Infect Dis. 2022 May;28(5):1062-1064. doi: 10.3201/eid2805.212517.

Le Ray LF, Aubry A, Sougakoff W, Revest M, Robert J, Bonnet I, Veziris N, Morel F.

We report the emergence of an atpE mutation in a clinical Mycobacterium tuberculosis strain. Genotypic and phenotypic bedaquiline susceptibility testing displayed variable results over time and ultimately were not predictive of treatment outcome. This observation highlights the limits of current genotypic and phenotypic methods for detection of bedaquiline resistance.

DOI: 10.3201/eid2805.212517
PMCID: PMC9045433
PMID: 35447056 [Indexed for MEDLINE]

78. **Fluorescence Biosensor for One-Step Simultaneous Detection of Mycobacterium tuberculosis Multidrug-Resistant Genes Using nanoCoTPyP and Double Quantum Dots**.

Anal Chem. 2022 May 20. doi: 10.1021/acs.analchem.2c00723. Online ahead of print.

Hu O(1), Li Z(1), He Q(1), Tong Y(2), Tan Y(3), Chen Z(1).

The diagnosis of multidrug-resistant tuberculosis (MDR-TB) is crucial for the subsequent drug guidance to improve therapy and control the spread of this infectious disease. Herein, we developed a novel florescence biosensor for simultaneous detection of Mycobacterium tuberculosis (Mtb) multidrug-resistant genes (rpoB531 for rifampicin and katG315 for isoniazid) by using our synthesized nanocobalt 5,10,15,20-tetra(4-pyridyl)-21H,23H-porphine (nanoCoTPyP) and double quantum dots (QDs). Several nanoCoTPyPs with different charges and morphology were successfully prepared via the surfactant-assisted method and their quenching ability and restoring efficiency for DNA detection were systematically analyzed. It was found that spherical nanoCoTPyP with positive charge exhibited excellent quenching effect and sensing performance for the two DNAs' detection due to its affinity differences towards single-stranded DNA (ssDNA) and double-stranded DNA (dsDNA). ssDNA attached on QDs (QDs-ssDNA) was specifically hybridized with targets to form QDs-dsDNA, resulting in fluorescence recovery due to the disruption of the interactions between nanoCoTPyP and ssDNA. Two drug-resistant genes could be simultaneously quantified in a single run and relatively low limits of detection (LODs) were obtained (24 pM for T1 and 20 pM for T2). Furthermore, the accuracy and reliability of our method were verified by testing clinical samples. This simple and low-cost approach had great potential to be applied in clinical diagnosis of MDR-TB.

DOI: 10.1021/acs.analchem.2c00723

PMID: 35594337

79. The Conflict in Ukraine: What Does It Mean for HIV and TB?

J Assoc Nurses AIDS Care. 2022 May-Jun 01;33(3):239-240. doi: 10.1097/JNC.0000000000000338. Epub 2022 Apr 13.

Relf MV(1).

DOI: 10.1097/JNC.0000000000000338
PMID: 35426855 [Indexed for MEDLINE]

80. Can you treat non-severe tuberculosis with a shorter regimen?

Arch Dis Child. 2022 May;107(5):435. doi: 10.1136/archdischild-2022-324256.

[No authors listed]

DOI: 10.1136/archdischild-2022-324256
PMID: 35443979 [Indexed for MEDLINE]

81. **Prolonged-course tuberculosis treatment or secondary prevention for those at high risk of recurrence?**

Clin Microbiol Infect. 2022 May;28(5):631-633. doi: 10.1016/j.cmi.2022.01.013. Epub 2022 Feb 3.

Moore DP(1), Hesseling AC(2), Marx FM(3).

Comment on
Clin Microbiol Infect. 2022 May;28(5):684-689.

DOI: 10.1016/j.cmi.2022.01.013
PMID: 35124263 [Indexed for MEDLINE]

82**. Investing in drug-resistant tuberculosis household contact management and preventive treatment.**

Lancet Glob Health. 2022 May 18:S2214-109X(22)00200-5. doi: 10.1016/S2214-109X(22)00200-5. Online ahead of print.

Hussain H(1), Malik AA(2).

DOI: 10.1016/S2214-109X(22)00200-5

PMID: 35597250

83. **Modification of bacterial cell membrane dynamics and morphology upon exposure to sub inhibitory concentrations of ciprofloxacin.**

Biochim Biophys Acta Biomembr. 2022 Aug 1;1864(8):183935. doi: 10.1016/j.bbamem.2022.183935. Epub 2022 Apr 21.

Ponmalar II(1), Swain J(2), Basu JK(3).

Ciprofloxacin (CPX), a second generation fluoroquinolone antibiotic, is used as a primary antibiotic for treatment against gastroenteritis, drug-resistant tuberculosis, and malignant otitis externa. CPX is a broad spectrum antibiotic that targets the DNA gyrase of both Gram-positive and Gram-negative bacteria. Irrational and improper usage of CPX results in emergence of CPX resistant organisms emphasizing the importance of using lethal doses of CPX. Here, we have systematically analysed the effect of CPX at sub lethal concentrations on live E. coli membrane and growth dynamics. As a result of CPX interaction at sub-lethal concentrations, we detected filamentation of the bacterial cells during cell division. Although CPX is a DNA targeting antibiotic and did not result in considerable increase of live E. coli cell surface roughness, we observed significant enhancement in the lipid diffusion coefficients possibly due to disrupted lipid packing or altered lipid composition. Interestingly, we seem to observe slightly higher extent of lipid diffusion alteration when bacterial inner membrane specific label FM4-64 was used in comparison to the non-specific membrane dye. Both these results are contrary to that observed in bacterial cells for colistin, a membrane targeting antibiotics. Our work highlights the need for using multiple, complementary surface and depth sensitive techniques to obtain information on the realistic nature of bacterial cell membrane remodelling due to non-membrane targeting antibiotics. Our work could have implications for identification of potential biomembrane markers at sub-lethal concentrations even for antibiotics which are non-membrane targeting that could help in unravelling pathways for emergence of antimicrobial resistance.

DOI: 10.1016/j.bbamem.2022.183935
PMID: 35461827 [Indexed for MEDLINE]

84**. Correction to: The dynamic impacts of Financial Investment on environmental-health and MDR-TB diseases and their influence on environmental sustainability at Chinese hospitals.**

Environ Sci Pollut Res Int. 2022 Apr 23. doi: 10.1007/s11356-022-20415-7. Online ahead of print.

Dai Z(1), Sadiq M(2), Kannaiah D(3), Khan N(4), Shabbir MS(5), Bilal K(6), Tabash MI(7).

Erratum for
Environ Sci Pollut Res Int. 2022 Mar 30;:

DOI: 10.1007/s11356-022-20415-7
PMID: 35460490

85**. Emerging impact of triazoles as anti-tubercular agent.**

Eur J Med Chem. 2022 May 13;238:114454. doi: 10.1016/j.ejmech.2022.114454. Online ahead of print.

Sharma A(1), Agrahari AK(2), Rajkhowa S(3), Tiwari VK(4).

Tuberculosis, a disease of poverty is a communicable infection with a reasonably high mortality rate worldwide. 10 Million new cases of TB were reported with approx 1.4 million deaths in the year 2019. Due to the growing number of drug-sensitive and drug-resistant tuberculosis cases, there is a vital need to develop new and effective candidates useful to combat this deadly disease. Despite tremendous efforts to identify a mechanism-based novel antitubercular agent, only a few have entered into clinical trials in the last six decades. In recent years, triazoles have been well explored as the most valuable scaffolds in drug discovery and development. Triazole framework possesses favorable properties like hydrogen bonding, moderate dipole moment, enhanced water solubility, and also the ability to bind effectively with biomolecular targets of M. tuberculosis and therefore this scaffold displayed excellent potency against TB. This review is an endeavor to summarize an up-to-date innovation of triazole-appended hybrids during the last 10 years having potential in vitro and in vivo antitubercular activity with structure activity relationship analysis. This review may help medicinal chemists to explore the triazole scaffolds for the rational design of potent drug candidates having better efficacy, improved selectivity and minimal toxicity so that these hybrid NCEs can effectively be explored as potential lead to fight against M. tuberculosis.

DOI: 10.1016/j.ejmech.2022.114454
PMID: 35597009

86**. Treatment interruption patterns and adverse events among patients on bedaquiline containing regimen under programmatic conditions in India.**

Pulmonology. 2022 May-Jun;28(3):203-209. doi: 10.1016/j.pulmoe.2020.09.006. Epub 2020 Oct 26.

Natarajan S(1), Singla R(2), Singla N(3), Gupta A(1), Caminero JA(4), Chakraborty A(1), Kumar V(1).

BACKGROUND: The study aimed to analyze frequency and severity of adverse events (AEs) and other reasons for interruption of treatment and loss to follow up (LTFU) during first six months of treatment among tuberculosis patients on bedaquiline containing regimens.
METHODS: This pilot exploratory observational study included 275 patients enrolled consecutively over two years who received bedaquiline containing regimen under programmatic conditions in India.
RESULTS: Among 275 patients with median age of 25 years, 86 (31.3%) patients had at least one interruption with 122 total episodes of interruption. Among these 70 were temporary, 35 were permanent interruptions and 17 were LTFU. The AEs due to drugs were the commonest reason for interruption observed in 81.4% of temporary interruption group and 97.1% of permanent interruption group. Among a total 192 adverse event episodes, (49.5%) were minor (grade 1-2) and (50.5%) were serious (grade 3-5). Personal factors were the commonest reason for interruption observed in LTFU (94.1%) group. The most common temporarily interrupted drug was bedaquiline in 8.7% and permanently stopped drug was linezolid in 5% of patients.
CONCLUSIONS: Our study observed that drug related AEs are important risk factors associated with treatment interruptions in bedaquiline containing regimens. Bedaquiline is the most common temporarily interrupted drug due to AEs.

DOI: 10.1016/j.pulmoe.2020.09.006
PMID: 33121945 [Indexed for MEDLINE]

87. **A Novel Approach of Targeting Linezolid Nanoemulsion for the Management of Lymph Node Tuberculosis.**

ACS Omega. 2022 Apr 25;7(18):15688-15694. doi: 10.1021/acsomega.2c00592. eCollection 2022 May 10.

Choudhary A(1), Jain P(1), Mohapatra S(1), Mustafa G(2), Ansari MJ(3), Aldawsari MF(3), Alalaiwe AS(3), Mirza MA(1), Iqbal Z(1).

Tuberculosis (TB) represents a major public health problem, globally affecting children and adults. Lymphatic TB is the most common type of extrapulmonary tuberculosis, which affects the peripheral lymph nodes. This burgeoning disease requires a long-term treatment of multiple antibiotics to kill Mycobacterium tuberculosis, resulting in an increased rate of multidrug-resistant tuberculosis. To overcome drug resistance with the first-line antibiotics, linezolid W/O nanoemulsion was developed in this current work. W/O nanoemulsion was prepared by oil phase titration technique using sunflower oil, span 80 and tween 80, and optimized by pseudophase ternary diagrams. The particle size, polydispersity index, zeta potential, viscosity, and refractive index for the optimized formulation were found to be 92.32 nm, 0.066, -21.9 mV, 32.623 cP, and 1.453, respectively. Drug release from the developed nanoemulsion followed the zero-order kinetic. The antimicrobial efficacy study confirms the antibacterial potential of the developed nanoemulsion. In vivo studies conducted on Wistar rats confirms the lymphatic targeting with a high amount of drug at the target organ just after 8 h of dosing. As a result of the foregoing promising results, it may be inferred that the suggested nanoemulsion could be a viable therapy option for lymph node tuberculosis.

DOI: 10.1021/acsomega.2c00592
PMCID: PMC9096948
PMID: 35571844

88. **Early Bactericidal Activity of Meropenem plus Clavulanate (with or without Rifampin) for Tuberculosis: The COMRADE Randomized, Phase 2A Clinical Trial.**

Am J Respir Crit Care Med. 2022 May 15;205(10):1228-1235. doi: 10.1164/rccm.202108-1976OC.

De Jager V(1), Gupte N(2)(3), Nunes S(1), Barnes GL(2), van Wijk RC(4), Mostert J(1), Dorman SE(5), Abulfathi AA(6)(7), Upton CM(1), Faraj A(4), Nuermberger EL(2), Lamichhane G(2), Svensson EM(8)(9), Simonsson USH(4), Diacon AH(1), Dooley KE(2).

Comment in
Am J Respir Crit Care Med. 2022 May 15;205(10):1142-1144.

Rationale: Carbapenems are recommended for treatment of drug-resistant tuberculosis. Optimal dosing remains uncertain. Objectives: To evaluate the 14-day bactericidal activity of meropenem, at different doses, with or without rifampin. Methods: Individuals with drug-sensitive pulmonary tuberculosis were

randomized to one of four intravenous meropenem-based arms: 2 g every 8 hours (TID) (arm C), 2 g TID plus rifampin at 20 mg/kg once daily (arm D), 1 g TID (arm E), or 3 g once daily (arm F). All participants received amoxicillin/clavulanate with each meropenem dose. Serial overnight sputum samples were collected from baseline and throughout treatment. Median daily fall in colony-forming unit (CFU) counts per milliliter of sputum (solid culture) (EBACFU0-14) and increase in time to positive culture (TTP) in liquid media were estimated with mixed-effects modeling. Serial blood samples were collected for pharmacokinetic analysis on Day 13. Measurements and Main Results: Sixty participants enrolled. Median EBACFU0-14 counts (2.5th-97.5th percentiles) were 0.22 (0.12-0.33), 0.12 (0.057-0.21), 0.059 (0.033-0.097), and 0.053 (0.035-0.081); TTP increased by 0.34 (0.21-0.75), 0.11 (0.052-0.37), 0.094 (0.034-0.23), and 0.12 (0.04-0.41) (log10 h), for arms C-F, respectively. Meropenem pharmacokinetics were not affected by rifampin coadministration. Twelve participants withdrew early, many of whom cited gastrointestinal adverse events. Conclusions: Bactericidal activity was greater with the World Health Organization-recommended total daily dose of 6 g daily than with a lower dose of 3 g daily. This difference was only detectable with solid culture. Tolerability of intravenous meropenem, with amoxicillin/clavulanate, though, was poor at all doses, calling into question the utility of this drug in second-line regimens. Clinical trial registered with www.clinicaltrials.gov (NCT03174184).

DOI: 10.1164/rccm.202108-1976OC
PMID: 35258443 [Indexed for MEDLINE]

89**. Update on the Coordinated Efforts of Looking After the Health Care Needs of Children and Young People Fleeing the Conflict Zone of Ukraine Presenting to European Emergency Departments-A Joint Statement of the European Society for Emergency Paediatrics and the European Academy of Paediatrics.**

Front Pediatr. 2022 Apr 26;10:897803. doi: 10.3389/fped.2022.897803. eCollection 2022.

Nijman RG(1)(2)(3), Bressan S(4), Brandenberger J(5)(6)(7), Kaur D(8), Keitel K(7)(9), Maconochie IK(1)(3), Oostenbrink R(10), Parri N(11), Shavit I(12), Teksam O(13), Velasco R(14), van de Voorde P(15), Da Dalt L(4), Guchtenaere A(16), Hadjipanayis AA(17), Ross Russell R(18), Del Torso S(19), Bognar Z(20), Titomanlio L(21)(22).

This joint statement by the European Society for Emergency Paediatrics and European Academy of Paediatrics aims to highlight recommendations for dealing with refugee children and young people fleeing the Ukrainian war when presenting to emergency departments (EDs) across Europe. Children and young people might present, sometimes unaccompanied, with either ongoing complex health needs or

illnesses, mental health issues, and injuries related to the war itself and the flight from it. Obstacles to providing urgent and emergency care include lack of clinical guidelines, language barriers, and lack of insight in previous medical history. Children with complex health needs are at high risk for complications and their continued access to specialist healthcare should be prioritized in resettlements programs. Ukraine has one of the lowest vaccination coverages in the Europe, and outbreaks of cholera, measles, diphtheria, poliomyelitis, and COVID-19 should be anticipated. In Ukraine, rates of multidrug resistant tuberculosis are high, making screening for this important. Urgent and emergency care facilities should also prepare for dealing with children with war-related injuries and mental health issues. Ukrainian refugee children and young people should be included in local educational systems and social activities at the earliest opportunity.

DOI: 10.3389/fped.2022.897803
PMCID: PMC9090499
PMID: 35558376

90. **Corrigendum to 'High prevalence of hepatitis C infection among multidrug-resistant tuberculosis patients' [J Hepatol 72 (2020) 1028-1029].**

J Hepatol. 2022 May 14:S0168-8278(22)00247-1. doi: 10.1016/j.jhep.2022.04.012. Online ahead of print.

Seung KJ(1), Franke MF(2), Hewison C(3), Huerga H(4), Khan U(5), Mitnick CD(6); endTB Study Group.

Erratum for
J Hepatol. 2020 May;72(5):1028-1029.

DOI: 10.1016/j.jhep.2022.04.012
PMID: 35581037

91**. A case of multidrug-resistant tuberculosis presenting as erythema elevatum diutinum: A rare association.**

Indian J Dermatol Venereol Leprol. 2022 May 4:1-3. doi: 10.25259/IJDVL_1062_2021. Online ahead of print.

Sinha P(1), Sharma J(1), Tiwari S(2), Bhattacharjee S(3), Sinha A(4).

DOI: 10.25259/IJDVL_1062_2021
PMID: 35593283

92**. A cross-sectional study to determine the psychological distress among pulmonary tuberculosis patients during COVID-19 pandemic.**

Monaldi Arch Chest Dis. 2022 May 13. doi: 10.4081/monaldi.2022.2255. Online ahead of print.

Mandal A(1), Verma AK(2), Verma SK(3), Kar SK(4), Bajpai J(5), Kant S(6), Kumar S(7), Kushwaha RAS(8), Garg R(9), Srivastava A(10), Bajaj DK(11), Chaudhary SC(12).

COVID-19 pandemic had adversely affected the services of the National Tuberculosis (TB) Elimination Programme, resulting in psychological distress among pulmonary tuberculosis patients (PTB). This cross-sectional, hospital-based study included 361 PTB patients. Three pre-defined questionnaires were used for the analysis, a questionnaire to evaluate anxiety related to COVID-19, a patient health questionnaire (PHQ-9) for depression, and a fear of COVID-19 scale (FCV-19S) questionnaire. Among 361 PTB patients, 13% (n=47) had COVID-19 infection. Out of the total patients, 69% (n=250) were DR-TB (drug resistance-tuberculosis) cases. Proportion of anxiety, fear and depression due to COVID-19 was found in 49% (n=177), 23% (n=83), 67% (n=247) respectively. Delay in the initiation of anti-tubercular treatment was found in 58% (n=210) of the cases, among which the majority, i.e., 69% (n=172, p=0.011), were DR-TB. This pandemic has led to a sudden step-down of PTB. Trend analysis of the psychological distress showed a peak following the COVID-19 pandemic. Most DR-TB patients had delayed initiation of the anti-tubercular treatment during the pandemic. The preponderance of the younger age group was seen in the pulmonary tuberculosis patients, and a majority of them had DR-TB. Depression was the predominant psychological distress among the study subjects during the pandemic.

DOI: 10.4081/monaldi.2022.2255
PMID: 35593023