Literature

1. Healthcare delivery for HIV-positive people with tuberculosis in Europe.

HIV Med. 2021 Apr;22(4):283-293. doi: 10.1111/hiv.13016. Epub 2020 Nov 20.

Bentzon AK(1), Panteleev A(2), Mitsura V(3), Borodulina E(4), Skrahina A(5), Denisova E(6), Tetradov S(7), Podlasin R(8), Riekstina V(9), Kancauskiene Z(10), Paduto D(11), Mocroft A(12), Trofimova T(13), Miller R(14), Post F(15), Grezesczuk A(16), Lundgren JD(1), Inglot M(17), Podlekareva D(1), Bolokadze N(18), Kirk O(1); TB:HIV Study Group.

BACKGROUND: In a 2013 survey, we reported distinct discrepancies in delivery of tuberculosis (TB) and HIV services in eastern Europe (EE) vs. western Europe (WE).
OBJECTIVES: To verify the differences in TB and HIV services in EE vs. WE.
METHODS: Twenty-three sites completed a survey in 2018 (EE, 14; WE, nine; 88% response rate). Results were compared across as well as within the two regions. When possible, results were compared with the 2013 survey.
RESULTS: Delivery of healthcare was significantly less integrated in EE: provision of TB and HIV services at one site (36% in EE vs. 89% in WE; P = 0.034), and continued TB follow-up in one location (42% vs. 100%; P = 0.007). Although access to TB diagnostics, standard TB and HIV drugs was generally good, fewer sites in EE reported unlimited access to rifabutin/multi-drug-resistant TB (MDR-TB) drugs, HIV integrase inhibitors and opioid substitution therapy (OST). Compared with 2013, routine usage of GeneXpert was more common in EE in 2018 (54% vs. 92%; P = 0.073), as was access to moxifloxacin (46% vs. 91%; P = 0.033), linezolid (31% vs. 64%; P = 0.217), and bedaquiline (0% vs. 25%; P = 0.217). Integration of TB and HIV services (46% vs. 39%; P = 1.000) and provision of OST to patients with opioid dependency (54% vs. 46%; P = 0.695) remained unchanged.
CONCLUSION: Delivery of TB and HIV healthcare, including integration of TB and HIV care and access to MDR-TB drugs, still differs between WE and EE, as well as between individual EE sites.

DOI: 10.1111/hiv.13016
PMID: 33215809

2. Early outcome and safety of bedaquiline-containing regimens for treatment of MDR- and XDR-TB in China: a multicentre study.

Clin Microbiol Infect. 2021 Apr;27(4):597-602. doi: 10.1016/j.cmi.2020.06.004. Epub 2020 Jun 15.

Gao M(1), Gao J(2), Xie L(1), Wu G(3), Chen W(4), Chen Y(5), Pei Y(6), Li G(7), Liu Y(2), Shu W(2), Fan L(8), Wu Q(9), Du J(10), Chen X(11), Tang P(12), Xiong Y(13), Li M(14), Cai Q(15), Jin L(16), Mei Z(17), Pang Y(18), Li L(19).

OBJECTIVES: Bedaquiline treatment significantly improves multidrug-resistant tuberculosis (MDR-TB) patient treatment outcomes. However, safety and efficacy data are lacking for bedaquiline used with background regimens to treat Chinese TB patients. Here, we describe our initial clinical experience for bedaquiline treatment of a large multicentre cohort of MDR-TB and extensively drug-resistant tuberculosis (XDR-TB) patients in China.
METHODS: Patients (177) received 24-week bedaquiline treatment combined with personalized anti-TB drug background regimens. As primary efficacy endpoints, times to initial sputum culture conversion were measured.
RESULTS: Of 177 MDR-TB patients completing the 24-week treatment course, sputum culture conversion occurred for 151/177 (85.3%), while 26 had unfavourable outcomes, including 3/177 (1.7%) deaths and 23/177 (13.0%) non-responders at treatment completion. The median time to sputum culture conversion was 4 (interquartile range 2-8) weeks. Conversion rates were 33/39 (84.6%, 95% confidence interval (CI) 73.3-95.9) for MDR-TB patients, 47/56 (83.9%, 95% CI 74.3-93.6) for pre-XDR-TB patients and 71/82 (86.6%, 95% CI 79.2-94.0) for XDR-TB patients. Multivariate analysis demonstrated that patients with low body mass index (odds ratio 7.356; 95% CI 2.652-20.401) were at significantly high risk of unfavourable outcomes, with serious adverse events noted in 15 (8.5%) patients, including six with corrected QT interval (QTc) prolongation times (>500 ms).
CONCLUSION: Bedaquiline, when included in background regimens for treatment of MDR-TB and XDR-TB patients in China, was safe and associated with a high rate of culture conversion.

DOI: 10.1016/j.cmi.2020.06.004
PMID: 32553880

3. Tuberculosis Drug Susceptibility, Treatment, and Outcomes for Belarusian HIV-Positive Patients with Tuberculosis: Results from a National and International Laboratory.

Tuberc Res Treat. 2021 Apr 2;2021:6646239. doi: 10.1155/2021/6646239.
eCollection 2021.

Podlekareva DN(1), Folkvardsen DB(2), Skrahina A(3), Vassilenko A(4), Skrahin A(3)(4), Hurevich H(3), Klimuk D(3), Karpov I(4), Lundgren JD(1), Kirk O(1)(5), Lillebaek T(2)(6).

BACKGROUND: To cure drug-resistant (DR) tuberculosis (TB), the antituberculous treatment should be guided by Mycobacterium tuberculosis drug-susceptibility testing (DST). In this study, we compared conventional DST performed in Minsk, Belarus, a TB DR high-burden country, with extensive geno- and phenotypic analyses performed at the WHO TB Supranational Reference Laboratory in Copenhagen, Denmark, for TB/HIV coinfected patients. Subsequently, DST results were related to treatment regimen and outcome.
METHODS: Thirty TB/HIV coinfected patients from Minsk were included and descriptive statistics applied.
RESULTS: Based on results from Minsk, 10 (33%) TB/HIV patients had drug-sensitive TB. Two (7%) had isoniazid monoresistant TB, 8 (27%) had multidrug-resistant (MDR) TB, 5 (17%) preextensive drug-resistant (preXDR) TB, and 5 (17%) had extensive drug-resistant (XDR) TB. For the first-line drugs rifampicin and isoniazid, there was DST agreement between Minsk and Copenhagen for 90% patients. For the second-line anti-TB drugs, discrepancies were more pronounced. For 14 (47%) patients, there were disagreements for at least one drug, and 4 (13%) patients were classified as having MDR-TB in Minsk but were classified as having preXDR-TB based on DST results in Copenhagen. Initially, all patients received standard anti-TB treatment with rifampicin, isoniazid, pyrazinamide, and ethambutol. However, this was only suitable for 40% of the patients based on DST. On average, DR-TB patients were changed to 4 (IQR 3-5) active drugs after 1.5 months (IQR 1-2). After treatment adjustment, the treatment duration was 8 months (IQR 2-11). Four (22%) patients with DR-TB received treatment for >18 months. In total, sixteen (53%) patients died during 24 months of follow-up.
CONCLUSIONS: We found high concordance for rifampicin and isoniazid DST between the Minsk and Copenhagen laboratories, whereas discrepancies for second-line drugs were more pronounced. For patients with DR-TB, treatment was often insufficient and relevant adjustments delayed. This example from Minsk, Belarus, underlines two crucial points in the management of DR-TB: the urgent need for implementation of rapid molecular DSTs and availability of second-line drugs in all DR-TB high-burden settings. Carefully designed individualized treatment regimens in accordance with DST patterns will likely improve patients' outcome and reduce transmission with drug-resistant Mycobacterium tuberculosis strains.

DOI: 10.1155/2021/6646239
PMCID: PMC8035031
PMID: 33868727

4. Evaluating bedaquiline as a treatment option for multidrug-resistant tuberculosis.

Expert Opin Pharmacother. 2021 Apr;22(5):535-541. doi: 10.1080/14656566.2020.1867538. Epub 2021 Jan 4.

Martín-García M(1), Esteban J(1).

Introduction: Despite efforts to the contrary, tuberculosis remains one of the leading causes of death in the world. The appearance of multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains of Mycobacterium tuberculosis has increased the need for new therapeutic options against these strains.Areas covered: This review covers the in vitro susceptibility, pharmacokinetics, and pharmacodynamics of bedaquiline, a new drug shown to be active against M. tuberculosis-resistant strains. The authors further review clinical data concerning its use against MDR and XDR strains, discussing recent clinical guidelines from different international societies.Expert opinion: Available data demonstrate the usefulness of bedaquiline against resistant M. tuberculosis. Despite the difficulty in analyzing multidrug therapies, the use of bedaquiline in MDR and XDR tuberculosis increases success rates, allowing shortened treatments and lower drug use than previously recommended regimens. Moreover, the fact that MDR and XDR strains are common in many places creates a need to include this drug in the currently available protocols. It is essential to overcome the substantial barriers that some countries encounter in obtaining bedaquiline, as doing so will make therapeutic regimens including this drug available for all patients.

DOI: 10.1080/14656566.2020.1867538
PMID: 33393406

5. Pretomanid: The latest USFDA-approved anti-tuberculosis drug.

Indian J Tuberc. 2021 Apr;68(2):287-291. doi: 10.1016/j.ijtb.2020.09.003. Epub 2020 Sep 6.

Deb U(1), Biswas S(2).

Pretomanid is a nitroimidazooxazine drug which inhibits synthesis of mycolic

acid. This leads to defective cell wall formation, ultimately causing bacterial cell death. It is active against both replicating and non-replicating M. tuberculosis. Following promising result in a phase III trial, pretomanid was approved by United States Food and Drug Administration in August 2019. This orally active drug has been approved as part of a combination regimen of bedaquiline, pretomanid and linezolid (BPaL regimen) to treat adults with pulmonary extensive drug resistant tuberculosis (TB) or treatment-intolerant or non-responsive multidrug resistant TB. Peripheral neuropathy and increased liver enzymes are some of the reported adverse events associated with pretomanid. However, more studies are required to confirm the role of pretomanid in paediatric, geriatric and HIV co-infection cases.

DOI: 10.1016/j.ijtb.2020.09.003
PMID: 33845969

6. Evaluation of drug-resistant tuberculosis treatment outcome in Portugal, 2000-2016.

PLoS One. 2021 Apr 20;16(4):e0250028. doi: 10.1371/journal.pone.0250028. eCollection 2021.

Oliveira O(1)(2)(3), Gaio R(4)(5), Correia-Neves M(1)(2), Rito T(1)(2)(6), Duarte R(3)(7)(8).

Treatment of drug-resistant tuberculosis (TB), which is usually less successful than that of drug-susceptible TB, represents a challenge for TB control and elimination. We aimed to evaluate treatment outcomes and to identify the factors associated with death among patients with MDR and XDR-TB in Portugal. We assessed MDR-TB cases reported for the period 2000-2016, using the national TB Surveillance System. Treatment outcomes were defined according to WHO recommendations. We identified the factors associated with death using logistic regression. We evaluated treatment outcomes of 294 MDR- and 142 XDR-TB patients. The treatment success rate was 73.8% among MDR- and 62.7% among XDR-TB patients ($p = 0.023$). The case-fatality rate was 18.4% among MDR- and 23.9% among XDR-TB patients. HIV infection (OR 4.55; 95% CI 2.31-8.99; $p < 0.001$) and resistance to one or more second-line injectable drugs (OR 2.73; 95% CI 1.26-5.92; $p = 0.011$) were independently associated with death among MDR-TB patients. HIV infection, injectable drug use, past imprisonment, comorbidities, and alcohol abuse are conditions that were associated with death early on and during treatment. Early diagnosis of MDR-TB and further monitoring of these patients are necessary to

improve treatment outcome.

DOI: 10.1371/journal.pone.0250028
PMID: 33878119

7. Genetic variability in multidrug-resistant Mycobacterium tuberculosis isolates from patients with pulmonary tuberculosis in North India.

BMC Microbiol. 2021 Apr 21;21(1):123. doi: 10.1186/s12866-021-02174-6.

Singh AV(1), Singh S(2), Yadav A(2), Kushwah S(2), Yadav R(2), Sai DK(2), Chauhan DS(2).

BACKGROUND: Information on the genetic variability of drug resistant isolates of Mycobacterium tuberculosis is of paramount importance to understand transmission dynamics of disease and to improve TB control strategies. Despite of largest number of multidrug-resistant (MDR) tuberculosis cases (1, 30,000; 27% of the global burden), strains responsible for the expansion or development of drug-resistant Mycobacterium tuberculosis infections have been poorly characterized in India. Present study was aimed to investigate the genetic diversity in MDR isolates of Mycobacterium tuberculosis in North India.
RESULTS: Spacer oligonucleotide typing (spoligotyping) was performed on 293 clinical MDR isolates of Mycobacterium tuberculosis recovered from cases of pulmonary tuberculosis from North India. Spoligotyping identified 74 distinct spoligotype patterns. Comparison with an international spoligotype database (spoldb4 database) showed that 240 (81.91%) and 32 (10.92%) strains displayed known and shared type patterns, while 21 (7.16%) strains displayed unique spoligotype patterns. Among the phylogeographic lineages, lineage 3 (East African-Indian) was found most predominant lineage (n = 159, 66.25%), followed by lineage 2 (East Asian; n = 34, 14.16%), lineage 1 (Indo-Oceanic; n = 30, 12.50%) and lineage 4 (Euro American; n = 17, 7.08%). Overall, CAS1_DEL (60.41%; SITs 2585, 26, 2694, 309, 381, 428, 1401, 141, 25, 1327) was found most pre-dominant spoligotype pattern followed by Beijing (14.16%; SITs255, 260, 1941, 269) and EAI3_IND (5.00%; SITs 298, 338, 11). The demographic and clinical characteristics were not found significantly associated with genotypic lineages of MDR-M.tuberculosis isolates recovered from pulmonary TB patients of North India.
CONCLUSIONS: Present study reveals high genetic diversity among the Mycobacterium tuberculosis isolates and highlights that SIT141/CAS1_Del followed by SIT26/ Beijing lineage is the most common spoligotype responsible for the development and transmission of MDR-TB in North India. The high presence of shared type and unique spoligotype patterns of MDR strains indicates epidemiological significance of locally evolved strains in ongoing transmission

of MDR-TB within this community which needs to be further monitored using robust molecular tools with high discriminatory power.

DOI: 10.1186/s12866-021-02174-6
PMID: 33879047

8. Evaluation of magnesium oxide and zinc oxide nanoparticles against multi-drug-resistance Mycobacterium tuberculosis.

Indian J Tuberc. 2021 Apr;68(2):195-200. doi: 10.1016/j.ijtb.2020.07.032. Epub 2020 Aug 4.

Yaghubi Kalurazi T(1), Jafari A(2).

OBJECTIVE: The current study has evaluated the MICs and MBCs of ZnONPs, MgONPs, and MgONPs-ZnONPs against H37Rv Mtb and MDR-Mtb.
METHODS: Mixture, magnesium oxide nanoparticles (NPs) and zinc oxide (MgONPs-ZnONPs) were prepared. The microplate alamar blue (MABA) assay and the proportion method were used to evaluate of anti-tubercular activity against MDR-MTB. MTT test was done to MgONPs-ZnONPs against Vero and HepG2 cell lines.
RESULTS: The MIC of MgONPs and ZnONPs were 0.195 and 0.468 μg mL-1 against 104 of H37Rv Mtb. As well, 0.166 μg mL-1 of MgONPs-ZnONPs was able to inhibit 10-4 H37Rv Mtb. The MIC of MgONPs against 104 concentrations of MDR-Mtb was 12.5 μg mL-1. The MIC of MgONPs/ZnONPs against 104 concentrations of MDR-Mtb reached to 0.664 μg mL-1. The MBC value of ZnONPs increased to 1.875 μg mL-1 against 10-4 concentrations of MDR-Mtb. Testing showed that the MBCs of MgONPs/ZnONPs reached to 1.328 μg mL-1 against 104 concentrations of MDR-Mtb. The IC50 against MDR-TB was 0.779 μg mL-1 for ZnONPs and 0.883 μg mL-1 for MgONPs-ZnONPs. The MgONPs-ZnONPs was not toxic to Vero cell lines however ZnONPs could inhibit the Vero and HepG2 cell lines.
CONCLUSION: We found that ZnONPs and mixture MgONPs-ZnONPs not only have higher bactericide behavior but might have also synergistic effects against MDR-TB.

DOI: 10.1016/j.ijtb.2020.07.032
PMID: 33845951

9. Development and validation of a liquid chromatography-tandem mass spectrometry method for quantifying delamanid and its metabolite in small hair samples.

J Chromatogr B Analyt Technol Biomed Life Sci. 2021 Apr 15;1169:122467. doi: 10.1016/j.jchromb.2020.122467. Epub 2020 Dec 10.

Reckers A(1), Huo S(2), Esmail A(3), Dheda K(3), Bacchetti P(4), Gandhi M(5), Metcalfe J(6), Gerona R(7).

New all-oral regimens for rifampin-resistant tuberculosis (RR-TB) are being scaled up globally. Measurement of drug concentrations in hair assesses long-term drug exposure. Delamanid (DLM) is likely to be a key component of future RR-TB treatment regimens, but a method to describe its quantification in hair via liquid chromatography-tandem mass spectrometry (LC-MS/MS) has not previously been described. We developed and validated a simple, fast, sensitive, and accurate LC-MS/MS method for quantifying DLM and its metabolite DM-6705 in small hair samples. We pulverized and extracted two milligrams of hair in methanol at 37 °C for two hours, and diluted 1:1 with water. A gradient elution method eluted DLM, DM-6705, and the internal standard OPC 14714 within 3 min, bringing overall analysis time to 5.5 min. The method has limits of detection (LOD) of 0.0003 ng/mg for DLM and 0.003 ng/mg for DM-6705. The established linear dynamic ranges are 0.003-2.1 ng/mg and 0.03-21 ng/mg for DLM and DM-6705, respectively. Eleven of 12 participant hair samples had concentrations within DLM's linear dynamic range, while all 12 samples had concentrations within the quantifiable range for DM-6705. The ranges of concentrations observed in these clinical samples for DLM and DM-6705 were 0.004-0.264 ng/mg hair and 0.412-12.041 ng/mg hair respectively. We demonstrate that while DLM was detected in hair at very low levels, its primary metabolite DM-6705 had levels approximately 100 times higher. Measuring DM-6705 in hair may accurately reflect long-term adherence to DLM-containing regimens for drug-resistant TB.

DOI: 10.1016/j.jchromb.2020.122467
PMCID: PMC7987786
PMID: 33713954

10. Letter from Myanmar.

Respirology. 2021 Apr;26(4):396-397. doi: 10.1111/resp.13999. Epub 2021 Jan 2.

Thant YM(1).

DOI: 10.1111/resp.13999
PMID: 33389814

11. Multi-drug resistant tuberculosis, ten years later.

Med Clin (Barc). 2021 Apr 23;156(8):393-401. doi: 10.1016/j.medcli.2020.08.018. Epub 2021 Jan 31.

[Article in English, Spanish]

Caminero Luna JA(1), Pérez Mendoza G(2), Rodríguez de Castro F(2).

DOI: 10.1016/j.medcli.2020.08.018
PMID: 33531151

12. Treatment outcomes of patients with multidrug and extensively drug-resistant tuberculosis in Zhejiang, China.

Eur J Med Res. 2021 Apr 3;26(1):31. doi: 10.1186/s40001-021-00502-0.

Zhang MW(1), Zhou L(1), Zhang Y(1), Chen B(1), Peng Y(1), Wang F(1), Liu ZW(1), Wang XM(2), Chen SH(3).

BACKGROUND: The aim of this study was to assess the treatment outcomes of multidrug and extensively drug-resistant tuberculosis (M/XDR-TB) in Zhejiang, China and to evaluate possible risk factors associated with poor outcomes of M/XDR-TB.
METHODS: Two-hundred-and-sixty-two patients having M/XDR-TB who received the diagnosis and treatment at nine referral hospitals from 1 January 2016 to 31 December 2016 in Zhejiang, China were included. All patients received second-line regimens recommended by WHO under the DOTS-Plus strategy.
RESULTS: Among the 262 patients, the treatment success rate was 55.34% (n = 145) with 53.44% (n = 140) cured and 1.91% (n = 5) who completed treatment, 62 (23.66%) failed, 27 (10.31%) died, 16 (6.11%) defaulted and 12 (4.58%) transferred out. Forty (64.52%) of the 62 M/XDR-TB patients who failed treatment were due to adverse effects in the first 10 months of treatment. Eighteen patients (6.37%) had XDR-TB. Treatment failure was significantly higher among patients with XDR-TB at 50% than that among patients with non-XDR-TB at 21.72% (P = 0.006). Failure outcomes were associated with a baseline weight less than 50 kg (OR, 8.668; 95% CI 1.679-44.756; P = 0.010), age older than 60 years (OR, 9.053; 95% CI 1.606-51.027; P = 0.013), hemoptysis (OR, 8.928; 95% CI 1.048-76.923; P = 0.045), presence of cavitary diseases (OR, 10.204; 95% CI 2.032-52.631; P = 0.005), or treatment irregularity (OR, 47.619; 95% CI 5.025-500; P = 0.001).

CONCLUSION: Treatment outcomes for M/XDR-TB under the DOTS-Plus strategy in Zhejiang, China were favorable but still not ideal. Low body weight (< 50 kg), old age (> 60 years), severe symptoms of TB including cavitary disease, hemoptysis and irregular treatment were independent prognostic factors for failure outcomes in patients with M/XDR-TB.

DOI: 10.1186/s40001-021-00502-0
PMCID: PMC8019161
PMID: 33812390

13. The Treatment of Tuberculosis.

Clin Pharmacol Ther. 2021 Apr 10. doi: 10.1002/cpt.2261. Online ahead of print.

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

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

DOI: 10.1002/cpt.2261
PMID: 33837535

14. Treatment Outcomes of Extensively Drug-Resistant Tuberculosis in Pakistan: A Countrywide Retrospective Record Review.

Front Pharmacol. 2021 Mar 31;12:640555. doi: 10.3389/fphar.2021.640555. eCollection 2021.

Abubakar M(1), Ahmad N(1), Ghafoor A(2), Latif A(3), Ahmad I(4), Atif M(5), Saleem F(1), Khan S(6), Khan A(7), Khan AH(8).

Background: The current study is conducted with the aim to the fill the gap of information regarding treatment outcomes and variables associated with unsuccessful outcome among XDR-TB patients from Pakistan. Methods: A total of 404 culture confirmed XDR-TB patients who received treatment between 1st May 2010 and June 30, 2017 at 27 treatment centers all over Pakistan were retrospectively followed until their treatment outcomes were reported. A p-value <0.05 reflected a statistical significant association. Results: The patients had a mean age 32.9 ± 14.1 years. The overall treatment success rate was 40.6% (95% confidence interval [CI]:35.80-45.60%). A total of 155 (38.4%) patients were declared cured, 9 (2.2%) completed treatment, 149 (36.9%) died, 60 (14.9%) failed treatment and 31 (7.7%) were lost to follow up (LTFU). The results of the multivariate binary logistic regression analysis revealed that the patients' age of >60 years (OR = 4.69, 95%CI:1.57-15.57) and receiving high dose isoniazid (OR = 2.36, 95%CI:1.14-4.85) had statistically significant positive association with death, whereas baseline body weight >40 kg (OR = 0.43, 95%CI:0.25-0.73) and sputum culture conversion in the initial two months of treatment (OR = 0.33, 95%CI:0.19-0.58) had statistically significant negative association with death. Moreover, male gender had statistically significant positive association (OR = 1.92, 95%CI:1.04-3.54) with LTFU. Conclusion: The treatment success rate (40.6%) of XDR-TB patients in Pakistan was poor. Providing special attention and enhanced clinical management to patients with identified risk factors for death and LTFU in the current cohort may improve the treatment outcomes.

DOI: 10.3389/fphar.2021.640555
PMCID: PMC8044444
PMID: 33867989

15. Drug-Resistant Mycobacterium tuberculosis Isolates from New and Previously Treated TB Patients in China, 2017-2019.

Rev Soc Bras Med Trop. 2021 Mar 22;54:e0728-2020. doi: 10.1590/0037-8682-0728-2020. eCollection 2021.

Chun ZM(1), Jun JQ(2).

INTRODUCTION: Mycobacterium tuberculosis (MTB) is a causative agent of tuberculosis (TB) that causes death worldwide.
METHODS: MTB was subjected to phenotypic drug-susceptibility tests (DST), and drug-resistant genes were sequenced.
RESULTS: Previously treated patients were more likely to have positive smear results and exhibit drug resistance. New patients were more likely to be mono SM-resistant and less likely to be INH- and RIF-resistant. The most common mutations were katG (S315T), rpoB (S450L), rpsL (K43R), and embB (M306V).
CONCLUSIONS: The proportion of mono-SM-resistant TB among new patients was higher.

DOI: 10.1590/0037-8682-0728-2020
PMCID: PMC8008859
PMID: 33759925 [Indexed for MEDLINE]

16. Safety and immunogenicity of the adjunct therapeutic vaccine ID93 + GLA-SE in adults who have completed treatment for tuberculosis: a randomised, double-blind, placebo-controlled, phase 2a trial.

Lancet Respir Med. 2021 Apr;9(4):373-386. doi: 10.1016/S2213-2600(20)30319-2. Epub 2020 Dec 8.

Day TA(1), Penn-Nicholson A(2), Luabeya AKK(2), Fiore-Gartland A(3), Du Plessis N(4), Loxton AG(4), Vergara J(1), Rolf TA(1), Reid TD(2), Toefy A(2), Shenje J(2), Geldenhuys H(2), Tameris M(2), Mabwe S(2), Bilek N(2), Bekker LG(5), Diacon A(6), Walzl G(4), Ashman J(1), Frevol A(1), Sagawa ZK(1), Lindestam Arlehamn C(7), Sette A(7), Reed SG(1), Coler RN(8), Scriba TJ(2), Hatherill M(9); TBVPX-203 study team.

BACKGROUND: A therapeutic vaccine that prevents recurrent tuberculosis would be a major advance in the development of shorter treatment regimens. We aimed to assess the safety and immunogenicity of the ID93 + GLA-SE vaccine at various doses and injection schedules in patients with previously treated tuberculosis.
METHODS: This randomised, double-blind, placebo-controlled, phase 2a trial was conducted at three clinical sites near Cape Town, South Africa. Patients were recruited at local clinics after receiving 4 months of tuberculosis treatment, and screened for eligibility after providing written informed consent.

Participants were aged 18-60 years, BCG-vaccinated, HIV-uninfected, and diagnosed with drug-sensitive pulmonary tuberculosis. Eligible patients had completed standard treatment for pulmonary tuberculosis in the past 28 days. Participants were enrolled after completing standard treatment and randomly assigned sequentially to receive vaccine or placebo in three cohorts: 2 μg intramuscular ID93 + 2 μg GLA-SE on days 0 and 56 (cohort 1); 10 μg ID93 + 2 μg GLA-SE on days 0 and 56 (cohort 2); 2 μg ID93 + 5 μg GLA-SE on days 0 and 56 and placebo on day 28 (cohort 3); 2 μg ID93 + 5 μg GLA-SE on days 0, 28, and 56 (cohort 3); or placebo on days 0 and 56 (cohorts 1 and 2), with the placebo group for cohort 3 receiving an additional injection on day 28. Randomisation was in a ratio of 3:1 for ID93 + GLA-SE and saline placebo in cohorts 1 and 2, and in a ratio of 3:3:1 for (2 ×) ID93 + GLA-SE, (3 ×) ID93 + GLA-SE, and placebo in cohort 3. The primary outcomes were safety and immunogenicity (vaccine-specific antibody response and T-cell response). For the safety outcome, participants were observed for 30 min after each injection, injection site reactions and systemic adverse events were monitored until day 84, and serious adverse events and adverse events of special interest were monitored for 6 months after the last injection. Vaccine-specific antibody responses were measured by serum ELISA, and T-cell responses after stimulation with vaccine antigens were measured in cryopreserved peripheral blood mononuclear cells specimens using intracellular cytokine staining followed by flow cytometry. This study is registered with ClinicalTrials.gov, number NCT02465216.

FINDINGS: Between June 17, 2015, and May 30, 2016, we assessed 177 patients for inclusion. 61 eligible patients were randomly assigned to receive: saline placebo (n=5) or (2 ×) 2 μg ID93 + 2 μg GLA-SE (n=15) on days 0 and 56 (cohort 1); saline placebo (n=2) or (2 ×) 10 μg ID93 + 2 μg GLA-SE (n=5) on days 0 and 56 (cohort 2); saline placebo (n=5) on days 0, 28 and 56, or 2 μg ID93 + 5 μg GLA-SE (n=15) on days 0 and 56 and placebo injection on day 28, or (3 ×) 2 μg ID93 + 5 μg GLA-SE (n=14) on days 0, 28, and 56 (cohort 3). ID93 + GLA-SE induced robust and durable antibody responses and specific, polyfunctional CD4 T-cell responses to vaccine antigens. Two injections of the 2 μg ID93 + 5 μg GLA-SE dose induced antigen-specific IgG and CD4 T-cell responses that were significantly higher than those with placebo and persisted for the 6-month study duration. Mild to moderate injection site pain was reported after vaccination across all dose combinations, and induration and erythema in patients given 2 μg ID93 + 5 μg GLA-SE in two or three doses. One participant had grade 3 erythema and induration at the injection site. No vaccine-related serious adverse events were observed.

INTERPRETATION: Vaccination with ID93 + GLA-SE was safe and immunogenic for all tested regimens. These data support further evaluation of ID93 + GLA-SE in therapeutic vaccination strategies to improve tuberculosis treatment outcomes.

FUNDING: Wellcome Trust (102028/Z/13/Z).

DOI: 10.1016/S2213-2600(20)30319-2
PMID: 33306991 [Indexed for MEDLINE]

17. Spatial clustering of drug-resistant tuberculosis in Hunan province, China: an ecological study.

BMJ Open. 2021 Apr 1;11(4):e043685. doi: 10.1136/bmjopen-2020-043685.

Alene KA(1)(2), Xu Z(3), Bai L(4), Yi H(5), Tan Y(5), Gray D(6), Viney K(6)(7)(8), Clements AC(9)(2).

OBJECTIVE: This study aimed to investigate the spatial distribution of drug-resistant tuberculosis (DR-TB) in Hunan province, China.
METHODS: An ecological study was conducted using DR-TB data collected from the Tuberculosis Control Institute of Hunan Province between 2012 and 2018. Spatial clustering of DR-TB was explored using the Getis-Ord statistic. A Poisson regression model was fitted with a conditional autoregressive prior structure, and with posterior parameters estimated using a Bayesian Markov chain Monte Carlo simulation, to quantify associations with possible risk factors and identify clusters of high DR-TB risk.
RESULTS: A total of 2649 DR-TB patients were reported to Hunan TB Control Institute between 2012 and 2018. The majority of the patients were male (74.8%, n=1983) and had a history of TB treatment (88.53%, n=2345). The proportion of extensively DR-TB among all DR-TB was 3.3% (95% CI 2.7% to 4.1%), which increased from 2.8% in 2012 to 4.4% in 2018. Of 1287 DR-TB patients with registered treatment outcomes, 434 (33.8%) were cured, 198 (15.3%) completed treatment, 92 (7.1%) died, 108 (8.3%) had treatment failure and 455 (35.3%) were lost to follow-up. Half (50.9%, n=655) had poor treatment outcomes. The annual cumulative incidence rate of notified DR-TB increased over time from 0.25 per 100 000 people in 2012 to 0.83 per 100 000 people in 2018. Substantial spatial heterogeneity was observed, and hotspots were detected in counties located in the North and East parts of Hunan province. The cumulative incidence of notified DR-TB was significantly associated with urban communities.
CONCLUSION: The annual incidence of notified DR-TB increased over time in Hunan province. Spatial clustering of DR-TB was detected and significantly associated with urbanisation. This finding suggests that targeting interventions to the highest risk areas and population groups would be effective in reducing the burden and ongoing transmission of DR-TB.

DOI: 10.1136/bmjopen-2020-043685
PMID: 33795303

18. Dynamic needs and challenges of people with drug-resistant tuberculosis and HIV in South Africa: a qualitative study.

Lancet Glob Health. 2021 Apr;9(4):e479-e488. doi: 10.1016/S2214-109X(20)30548-9.

Daftary A(1), Mondal S(2), Zelnick J(3), Friedland G(4), Seepamore B(5), Boodhram R(6), Amico KR(7), Padayatchi N(6), O'Donnell MR(8).

Comment in
Lancet Glob Health. 2021 Apr;9(4):e381-e382.

BACKGROUND: There is little evidence of patient acceptability for drug-resistant tuberculosis (DRTB) care in the context of new treatment regimens and HIV co-infection. We aim to describe experiences of DRTB-HIV care among patients in KwaZulu-Natal province, South Africa.
METHODS: In this qualitative study using Bury's framework for chronic illness, we conducted 13 focus groups at a tertiary hospital with 55 patients co-infected with DRTB and HIV (28 women, 27 men) who were receiving new bedaquiline-based treatment for DRTB, concurrent with antiretroviral therapy. Eligible patients were consenting adults (aged >18 years) with confirmed DRTB and HIV who were enrolled into the PRAXIS study within 2 weeks of initiating bedaquiline-based treatment for DRTB. Participants were recruited from the PRAXIS cohort to participate in a focus group based on their time in DRTB treatment: early (2-6 weeks after treatment initiation), middle (2-6 months after discharge or treatment initiation if never hospitalised), and late (>6 months after treatment initiation). Focus groups were carried out in isiZulu language, audio recorded, and translated to English within 4 weeks. Participants were asked about their experiences of DRTB and HIV care and treatment, and qualitative data were coded and thematically analysed.
FINDINGS: From March, 2017, to June, 2018, distinctive patient challenges were identified at four critical stages of DRTB care: diagnosis, marked by centralised hospitalisation, renunciation from routine life, systemic stigmatisation and, for patients with longstanding HIV, renewed destabilisation; treatment initiation, marked by side-effects, isolation, and social disconnectedness; discharge, marked by brief respite and resurgent therapeutic and social disruption; and continuity, marked by deepening socioeconomic challenges despite clinical recovery. The periods of diagnosis and discharge into the community were particularly difficult. Treatment information and agency in decision making was a persistent gap. Sources of stigmatisation shifted with movement between the hospital and community. Resilience was built by connecting

to peers, self-isolating, financial and material security, and a focus on recovery.
INTERPRETATION: People with DRTB and HIV undergo disruptive, life-altering experiences. The lack of information, agency, and social protections in DRTB care and treatment causes wider-reaching challenges for patients compared with HIV. Decentralised, community, peer-support, and differentiated care models for DRTB might be ameliorative and help to maximise the promise of new regimens.
FUNDING: US National Institutes of Health.
TRANSLATION: For the isiZulu translation of the abstract see Supplementary Materials section.

DOI: 10.1016/S2214-109X(20)30548-9
PMCID: PMC8009302
PMID: 33740409 [Indexed for MEDLINE]

19. Outcomes of multidrug-resistant tuberculosis treated with bedaquiline or delamanid.

Clin Infect Dis. 2021 Apr 10:ciab304. doi: 10.1093/cid/ciab304. Online ahead of print.

Hwang H(1), Kang H(2), Kwon YS(3), Jeon D(4), Shim TS(5), Yim JJ(1).

ACKGROUND: Since September 1, 2016, bedaquiline and delamanid have been administered for treatment of patients with multidrug-resistant/rifampicin-resistant tuberculosis after the official approval in South Korea. This study aimed to assess and compare the final treatment outcomes of patients who received bedaquiline with those of patients who received delamanid.
METHODS: This is a nationwide cohort study of patients with multidrug-resistant/rifampicin-resistant tuberculosis in whom bedaquiline or delamanid was administered from September 1, 2016, to February 28, 2018, after receiving the official approval in South Korea. Patients were classified into the bedaquiline and delamanid group according to the first used drug. We evaluated and compared the final treatment outcomes between the groups.
RESULTS: During the study period, 284 patients with multidrug-resistant/rifampicin-resistant tuberculosis were approved to use bedaquiline or delamanid and 260 were included in the final analysis; 119 (45.8%) and 141 patients (54.2%) were classified into bedaquiline and delamanid

groups, respectively. Among them, 30 patients (11.5%) exhibited additional resistance to second-line injectable drugs, 94 patients (36.2%) had additional resistance to fluoroquinolones, and 37 patients (14.2%) had resistance to both drugs. The overall treatment success rate was 79.2%. Initiation of bedaquiline rather than delamanid was not associated with treatment success (adjusted odds ratio = 0.671, 95% confidence interval = 0.350-1.285). Frequencies of adverse events were not significantly different between the two groups.
CONCLUSIONS: Initial choice of bedaquiline or delamanid did not make any significant difference in the final treatment outcome or the frequencies of adverse events among patients with multidrug-resistant/rifampicin-resistant tuberculosis.

DOI: 10.1093/cid/ciab304
PMID: 33837767

20. Molecular characterization of multidrug-resistant tuberculosis against levofloxacin, moxifloxacin, bedaquiline, linezolid, clofazimine, and delamanid in southwest of China.

BMC Infect Dis. 2021 Apr 8;21(1):330. doi: 10.1186/s12879-021-06024-8.

Zheng H(#)(1), He W(#)(2), Jiao W(1), Xia H(2), Sun L(1), Wang S(2), Xiao J(1), Ou X(2), Zhao Y(3), Shen A(4).

OBJECTIVES: To explore the drug susceptibility of levofloxacin (LFX), moxifloxacin (MFX), bedaquiline (BDQ), linezolid (LZD), clofazimine (CFZ) and delamanid (DLM) against multidrug resistant tuberculosis (MDR-TB) isolates from drug resistance survey of southwest China, and to illustrate the genetic characteristics of MDR-TB isolates with acquired drug resistance.
METHODS: A total of 339 strains were collected from smear-positive TB patients in the drug resistance survey of southwest China between January 2014 and December 2016. The MICs for the above mentioned drugs were determined for MDR-TB by conventional drug susceptibility testing. Genes related to drug resistance were amplified with their corresponding pairs of primers.
RESULTS: MDR was observed in 88 (26.0%; 88/339) isolates. LFX had the highest resistance rate (50.0%; 44/88), followed by MFX (38.6%; 34/88). The resistance rate to LZD, CFZ, and DLM was 4.5% (4/88), 3.4% (3/88), and 4.5% (4/88), respectively, and the lowest resistance rate was observed in BDQ (2.3%; 2/88). Of the 45 isolates resistant to LFX and MFX, the most prevalent resistance

mutation was found in gyrA with the substitution of codon 94 (34/45, 75.6%). Two strains with CFZ - BDQ cross resistance had a mutation in the Rv0678 gene. Of the four LZD resistant isolates, two carried mutations in rplC gene. For the four isolates resistant to DLM, one isolate had mutations in codon 318 of fbiC gene, and two isolates were with mutations in codon 81 of ddn gene. CONCLUSION: This study provided evidence of the usefulness of new anti-TB drugs in the treatment of MDR-TB in China.

DOI: 10.1186/s12879-021-06024-8
PMCID: PMC8028109
PMID: 33832459

21. Treatment outcomes and predictive factors for multidrug-resistant TB and HIV coinfection in Rio de Janeiro State, Brazil.

Int J Tuberc Lung Dis. 2021 Apr 1;25(4):292-298. doi: 10.5588/ijtld.20.0887.

Bhering M(1), Duarte R(2), Kritski A(3).

BACKGROUND: Brazil ranks 14th worldwide in the number of TB cases and 19th in terms of TB-HIV co-infected cases. This study aims at identifying clinical and demographic factors associated with unsuccessful treatment outcomes (loss to follow-up, treatment failure and death) of HIV-positive patients with multidrug-resistant TB (MDR-TB) in Rio de Janeiro State, Brazil.METHODS: This was a retrospective cohort study of MDR-TB cases notified from 2000 to 2016 in RJ. Cox proportional hazard regression models were used to assess risk factors associated with unsuccessful treatment in HIV-positive patients with MDR-TB.RESULTS: Among 2,269 patients, 156 (6.9%) were HIV-positive and had a higher proportion of unsuccessful treatment outcomes (52.6%) than HIV-negative cases (43.7%). All HIV-positive cases with extensively drug-resistant TB (XDR-TB) had unsuccessful treatment outcomes. Multivariate analysis shows that previous MDR-TB treatment (HR 1.97, 95% CI 1.22-3.18) and illicit drugs use (HR 1.68, 95% CI 1.01-2.78) were associated with a greater hazard of unsuccessful treatment outcomes, while 6-month culture conversion (HR 0.48, 95% CI 0.27-0.84) and use of antiretroviral therapy (ART) (HR 0.51, 95% CI 0.32-0.80) were predictors of reduced risk.CONCLUSIONS: Unsuccessful treatment was higher among HIV patients with MDR-TB than among HIV-negative patients. Prompt initiation of ART and effective interventions are necessary to improve treatment adherence and prevent retreatment cases.

DOI: 10.5588/ijtld.20.0887
PMID: 33762073

22. Accuracy of molecular drug susceptibility testing amongst tuberculosis patients in Karakalpakstan, Uzbekistan.

Trop Med Int Health. 2021 Apr;26(4):421-427. doi: 10.1111/tmi.13543. Epub 2021 Jan 20.

Gil H(1), Margaryan H(1), Azamat I(1), Ziba B(1), Bayram H(2), Nazirov P(3), Gomez D(4), Singh J(5), Zayniddin S(6), Parpieva N(7), Achar J(8)(9).

OBJECTIVES: In this retrospective study, we evaluated the diagnostic accuracy of molecular tests (MT) for the detection of DR-TB, compared to the gold standard liquid-based drug susceptibility testing (DST) in Karakalpakstan.
METHODS: A total of 6670 specimens received in the Republican TB No 1 Hospital Laboratory of Karakalpakstan between January and July 2017 from new and retreatment patients were analysed. Samples were tested using Xpert MTB/RIF and line probe assays (LPA) for the detection of mutations associated with resistance. The sensitivity and specificity of MTs were calculated relative to results based on DST.
RESULTS: The accuracy of MT for detection of rifampicin resistance was high, with sensitivity and specificity over 98%. However, we observed reduced sensitivity of LPA for detection of resistance; 86% for isoniazid (95% CI 82-90%), 86% for fluoroquinolones (95% CI 68-96%), 70% for capreomycin (95% CI 46-88%) and 23% for kanamycin (95% CI 13-35%).
CONCLUSIONS: We show that MTs are a useful tool for rapid and safe diagnosis of DR-TB; however, clinicians should be aware of their limitations. Although detection of rifampicin resistance was highly accurate, our data suggest that resistance mutations circulating in the Republic of Karakalpakstan for other drugs were not detected by the methods used here. This merits further investigation.

DOI: 10.1111/tmi.13543
PMID: 33406316

23. Patients' perceptions regarding multidrug-resistant tuberculosis and barriers to seeking care in a priority city in Brazil during COVID-19 pandemic: A qualitative study.

PLoS One. 2021 Apr 9;16(4):e0249822. doi: 10.1371/journal.pone.0249822. eCollection 2021.

Santos FLD(1), Souza LLL(1), Bruce ATI(1), Crispim JA(1), Arroyo LH(1), Ramos ACV(1), Berra TZ(1), Alves YM(1), Scholze AR(1), Costa FBPD(1), Martoreli Júnior JF(1), Moncaio ACS(2), Pinto IC(1), Arcêncio RA(1).

This study aimed to analyze the discourses of patients who were diagnosed with multidrug-resistant tuberculosis, the perception of why they acquired this health condition and barriers to seeking care in a priority city in Brazil during the COVID-19 pandemic. This was an exploratory qualitative study, which used the theoretical-methodological framework of the Discourse Analysis of French matrix, guided by the Consolidated Criteria for Reporting Qualitative Research. The study was conducted in Ribeirão Preto, São Paulo, Brazil. Seven participants were interviewed who were undergoing treatment at the time of the interview. The analysis of the participants' discourses allowed the emergence of four discursive blocks: (1) impact of the social determinants in the development of multidrug-resistant tuberculosis, (2) barriers to seeking care and difficulties accessing health services, (3) perceptions of the side effects and their impact on multidrug-resistant tuberculosis treatment, and (4) tuberculosis and COVID-19: a necessary dialogue. Through discursive formations, these revealed the determinants of multidrug-resistant tuberculosis. Considering the complexity involved in the dynamics of multidrug-resistant tuberculosis, advancing in terms of equity in health, that is, in reducing unjust differences, is a challenge for public policies, especially at the current moment in Brazil, which is of accentuated economic, political and social crisis. The importance of psychosocial stressors and the lack of social support should also be highlighted as intermediary determinants of health. The study has also shown the situation of COVID-19, which consists of an important barrier for patients seeking care. Many patients reported fear, insecurity and worry with regard to returning to medical appointments, which might contribute to the worsening of tuberculosis in the scenario under study.

DOI: 10.1371/journal.pone.0249822
PMCID: PMC8034748
PMID: 33836024 [Indexed for MEDLINE]

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

Int J Infect Dis. 2021 Apr 3:S1201-9712(21)00293-9. doi: 10.1016/j.ijid.2021.03.075. Online ahead of print.

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

KJ(5), Issayeva AM(6).

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

DOI: 10.1016/j.ijid.2021.03.075
PMID: 33823277

25. Multidrug-resistant tuberculosis patients expressing the HLA-DRB1*04 allele, and after treatment they show a low frequency of HLA-II+ monocytes and a chronic systemic inflammation.

Microb Pathog. 2021 Apr;153:104793. doi: 10.1016/j.micpath.2021.104793. Epub 2021 Feb 11.

Ocaña-Guzman R(1), Tellez-Navarrete NA(1), Preciado-Garcia M(1), Ponce-Gallegos MA(2), Buendia-Roldan I(3), Falfán-Valencia R(4), Chavez-Galan L(5).

Tuberculosis (TB) is an infectious disease caused by the bacilli Mycobacterium tuberculosis (Mtb); most TB patients are infected with strains of Mtb sensitive to first-line drugs (DS-TB), but in the last years has been increased the presence of multidrug-resistant TB (MDR-TB). HLA class II (HLA-II) is expressed on antigen-presenting cells and reported the association between HLA alleles and DS-TB in the Mexican population. We studied HLA-II + CD16+ monocytes frequency and its relation with a pro-inflammatory profile during DS-TB versus MDR-TB, both before as in response to anti-tuberculosis treatment. Peripheral blood was obtained from MDR-TB at the basal time (before use of therapy), 1, 3, and 8 months of anti-TB therapy (moTBt), whereas DS-TB at basal and 1 and 6 moTBt. Our data showed that contrary to DS-TB, MDR-TB patients have decreased the frequency

of HLA-II + monocytes and increased the pro-inflammatory CD16+ monocytes from basal time until 8 moTBt. Similarly, only MDR-TB patients still have a high plasma level of IFN-γ and TNF pro-inflammatory cytokines for a long-time, and although MDR-TB patients showed an increased level of the soluble form of TIM3 and GAL9 at baseline, those molecules decreased as a response to anti-TB therapy. Finally, our data indicated that MDR-TB displayed DRB1*04 allele, suggesting an association between the infection by multidrug-resistance Mtb strain and the presence of the DRB1*04 allele in Mexican TB patients.

DOI: 10.1016/j.micpath.2021.104793
PMID: 33582220

26. Tuberculosis (TB) in pregnancy - A review.

Eur J Obstet Gynecol Reprod Biol. 2021 Apr;259:167-177. doi: 10.1016/j.ejogrb.2021.02.016. Epub 2021 Feb 19.

Orazulike N(1), Sharma JB(2), Sharma S(3), Umeora OUJ(4).

Tuberculosis (TB) is a common infectious pathology especially in low-income countries, which may complicate pregnancy. Although pulmonary TB is more common in pregnancy than extra pulmonary TB (EPTB), EPTB is becoming more common especially in those living with human deficiency virus (HIV) co infection or have other comorbidities. The diagnosis of TB may be delayed in pregnancy due to the masking of its symptoms by those of pregnancy. If diagnosed and treated on time both pulmonary TB and EPTB are associated with excellent maternal and perinatal outcome. If, however, there is delay in diagnosis and treatment then there could be adverse maternal and fetal consequences like preterm labour, fetal growth restriction and even stillbirths. Similarly severe forms of TB like disseminated disease (miliary TB) or multi drug resistant TB (MDR TB) are associated with poor outcome. Diagnosis and management is same as in non-pregnant patients. Both drug sensitive pulmonary TB and EPTB are treated with four drugs (isoniazid, rifampicin, pyrazinamide and ethambutol) orally daily for 2 months followed by three drugs (isoniazid, rifampicin and ethambutol) orally daily for 4 months. Drug resistant TB is treated with second line drugs with caution, as some of these drugs are teratogenic. Optimum antenatal care and nutrition therapy along with anti-tuberculosis drugs provide for optimum maternal and perinatal outcome. This review discusses maternal and perinatal outcomes, diagnosis and management of pulmonary TB and extrapulmonary TB as well as perinatal tuberculosis.

DOI: 10.1016/j.ejogrb.2021.02.016
PMID: 33684671

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

Microb Drug Resist. 2021 Mar 31. doi: 10.1089/mdr.2020.0496. Online ahead of print.

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

Objective: Shaanxi is the most highly populated province with high burdens of tuberculosis in northwestern China. The aim of this study was to investigate the molecular characteristics and drug resistance of Mycobacterium tuberculosis isolates from Shaanxi province of China in 2018. Methods: Phenotypic drug susceptibility testing and spoligotyping methods were performed on 518 M. tuberculosis isolates; drug-resistant isolates were sequenced in 11 drug loci, including katG, inhA, oxyR-ahpC, rpoB, embB, rpsL, rrs1 (nucleotides 388-1084), gyrA, gyrB, rrs2 (nucleotides 1158-1674), and eis. Results: The prevalences of isoniazid, rifampicin, ethambutol, streptomycin, ofloxacin, and kanamycin resistance were 22.0%, 19.3%, 7.9%, 23.8%, 10.4%, and 3.3%, respectively. The Beijing family (82.8%) was the predominant genotype, followed by the T (9.3%), H (0.6%), CAS (0.4%), LAM (0.4%), and U (0.4%) families. The percentage of Beijing genotype in a central area (88.1%) was higher than in the south (77.3%) and the north area (80.1%) ($p < 0.05$), while the sex, age, and treatment history between Beijing and non-Beijing family were not statistically different. Mutation analysis found that the most prevalent mutations were katG315, rpoB531, embB306, rpsL43, gyrA94, and rrs1401; the Beijing family exhibited a high rate of isoniazid-resistant isolates carrying katG315 mutations ($p < 0.05$). Furthermore, compared with the phenotypic data, the sensitivities of isoniazid, rifampicin, ethambutol, streptomycin, ofloxacin, and kanamycin resistance by sequencing base on 11 loci were 85.1%, 94.0%, 53.7%, 74.8%, 77.8%, and 64.7%, respectively. Conclusions: Shaanxi has a serious epidemic of drug-resistant tuberculosis, Beijing family is the predominant genotype, and the distribution showed geographic diversity. The prevalence of Beijing genotypes has a tendency to promote the transmission of high-level isoniazid-resistant M. tuberculosis. Besides, the hot spot regions localized in the embB, rrs2, and eis gene appear not to serve as excellent biomarkers for predicting ethambutol and kanamycin resistance in Shaanxi.

DOI: 10.1089/mdr.2020.0496
PMID: 33794134

28. Assessing the impacts of short-course multidrug-resistant tuberculosis treatment in the Southeast Asia Region using a mathematical modeling approach.

PLoS One. 2021 Mar 26;16(3):e0248846. doi: 10.1371/journal.pone.0248846. eCollection 2021.

Han WM(1)(2), Mahikul W(3), Pouplin T(4)(5), Lawpoolsri S(1), White LJ(5)(6), Pan-Ngum W(1)(7).

This study aimed to predict the impacts of shorter duration treatment regimens for multidrug-resistant tuberculosis (MDR-TB) on both MDR-TB percentage among new cases and overall MDR-TB cases in the WHO Southeast Asia Region. A deterministic compartmental model was constructed to describe both the transmission of TB and the MDR-TB situation in the Southeast Asia region. The population-level impacts of short-course treatment regimens were compared with the impacts of conventional regimens. Multi-way analysis was used to evaluate the impact by varying programmatic factors (eligibility for short-course MDR-TB treatment, treatment initiation, and drug susceptibility test (DST) coverage). The model predicted that overall TB incidence will be reduced from 246 (95% credible intervals (CrI), 221-275) per 100,000 population in 2020 to 239 (95% CrI, 215-267) per 100,000 population in 2035, with a modest reduction of 2.8% (95% CrI, 2.7%-2.9%). Despite the slight reduction in overall TB infections, the model predicted that the MDR-TB percentage among newly notified TB infections will remain steady, with 2.4% (95% CrI, 2.1-2.9) in 2020 and 2.5% (95% CrI, 2.3-3.1) in 2035, using conventional MDR-TB treatment. With the introduction of short-course regimens to treat MDR-TB, the development of resistance can be slowed by 38.6% (95% confidence intervals (CI), 35.9-41.3) reduction in MDR-TB case number, and 37.6% (95% CI, 34.9-40.3) reduction in MDR-TB percentage among new TB infections over the 30-year period compared with the baseline using the standard treatment regimen. The multi-way analysis showed eligibility for short-course treatment and treatment initiation greatly influenced the impacts of short-course treatment regimens on reductions in MDR-TB cases and percentage resistance among new infections. Policies which promote the expansion of short-course regimens and early MDR-TB treatment initiation should be considered along with other interventions to tackle antimicrobial resistance in the region.

DOI: 10.1371/journal.pone.0248846
PMCID: PMC7997007
PMID: 33770104

29. Policy changes and the screening, diagnosis and treatment of drug-resistant tuberculosis patients from 2015 to 2018 in Zhejiang Province, China: a retrospective cohort study.

BMJ Open. 2021 Apr 12;11(4):e047023. doi: 10.1136/bmjopen-2020-047023.

Jiang W(1), Peng Y(2), Wang X(2), Elbers C(3), Tang S(4), Huang F(5), Chen B(6), Cobelens F(7).

OBJECTIVES: To examine changes in the screening, diagnosis, treatment and management of drug-resistant tuberculosis (DRTB) patients, and investigate the impacts of DRTB-related policies on patients of different demographic and socioeconomic characteristics.
DESIGN: A retrospective cohort study using registry data, plus a survey on DRTB-related policies.
SETTING: All prefecture-level Centres for Disease Control in Zhejiang Province, China.
MAIN OUTCOME MEASURES: Alongside the care cascade, we examined: (1) reported number of presumptive DRTB patients; (2) percentage of presumptive patients with drug susceptibility testing (DST) records; (3) percentage of DRTB/rifampicin-resistant (RR) patients registered; (4) percentage of RR/multidrug-resistant TB (MDRTB) patients that received anti-DRTB treatment; and (5) percentage of RR/MDRTB patients cured/completed treatment among those treated. Multivariate logistic regressions were conducted to explore the impacts of DRTB policies after adjusting for other factors.
RESULTS: The number of reported presumptive DRTB patients and the percentage with DST records largely increased during 2015-2018, and the percentage of registered patients who received anti-DRTB treatment also increased from 59.0% to 86.5%. Patients under the policies of equipping GeneXpert plus expanded criteria for DST had a higher likelihood of being registered compared with no GeneXpert (adjusted OR (aOR)=2.57, 95% CI: 1.20 to 5.51), while for treatment initiation the association was only significant when further expanding the registration criteria (aOR=2.38, 95% CI: 1.19 to 4.79). Patients with registered residence inside Zhejiang were more likely to be registered (aOR=1.96, 95% CI: 1.52 to 2.52), treated (aOR=3.83, 95% CI: 2.78 to 5.28) and complete treatment (aOR=1.92, 95% CI: 1.03 to 3.59) compared with those outside.
CONCLUSION: The policy changes on DST and registration have effectively improved DRTB case finding and care. Nevertheless, challenges remain in servicing vulnerable groups such as migrants and improving equity in the access to TB care. Future policies should provide comprehensive support for migrants to complete treatment at their current place of residence.

by BMJ.

DOI: 10.1136/bmjopen-2020-047023
PMID: 33846156

30. Disputed rpoB mutations in Mycobacterium tuberculosis and tuberculosis treatment outcomes.

Antimicrob Agents Chemother. 2021 Apr 12:AAC.01573-20. doi: 10.1128/AAC.01573-20. Online ahead of print.

Lin WH(1)(2), Lee WT(1)(2), Tsai HY(1)(2), Jou R(3)(2)(4).

Discordant results for Mycobacterium tuberculosis isolates with disputed mutations between genotypic drug susceptibility testing (DST) (gDST) and phenotypic DST (pDST) impact RIF-resistant (RR) and multidrug-resistant (MDR) tuberculosis (TB) treatments due to a lack of practical clinical guidelines. To investigate the role of disputed rpoB mutations in M. tuberculosis and TB treatment outcomes, initial isolates of 837 clinical RR or MDR-TB cases confirmed during 2014-2018 were retested using agar-based RIF pDST and rpoB gene sequencing. Minimum inhibitory concentrations (MICs) were determined for isolates with disputed rpoB mutations. Disputed rpoB mutations were identified in 77 (9.2%) M. tuberculosis isolates, including 50 (64.9%) and 14 (18.2%) phenotypic RIF- and rifabutin (RFB)-resistant isolates, respectively. The predominant single mutations were L533P (44.2%) and L511P (20.8%). Most of the isolates harboring L511P (87.5%), H526N (100%), D516Y (70.0%) and L533P (63.6%) mutations had MICs ≤1 mg/L, whereas isolates harboring H526L (75%) had MICs > 1 mg/L. Of the 63 cases with treatment outcomes, 11 (17.5%) cases died, 1 (1.6%) case transferred out and 51 (81%) cases had favorable outcomes, including 8 and 20 cases treated with standard-dose RIF- and RFB-containing regimens, respectively. Excluding cases transferred out, received no or 1-day treatment, we observed statistically significant differences between active and inactive fluoroquinolones (FQs) [P =0.004, Odds ratio =0.05 (95% confidence intervals, 0.01-0.38)] in 57 cases. We concluded that disputed rpoB mutations are not rare. Depending on resources, sequencing and/or MIC testing is recommended for better management of RR and MDR-TB cases.

DOI: 10.1128/AAC.01573-20
PMID: 33846134

31. Prolonged use of bedaquiline in two patients with pulmonary extensively

drug-resistant tuberculosis: Two case reports.

World J Clin Cases. 2021 Apr 6;9(10):2326-2333. doi: 10.12998/wjcc.v9.i10.2326.

Gao JT(1), Xie L(2), Ma LP(2), Shu W(1), Zhang LJ(1), Ning YJ(1), Xie SH(1), Liu YH(1), Gao MQ(3).

BACKGROUND: Bedaquiline is among the prioritized drugs recommended by the World Health Organization for the treatment of extensively drug-resistant tuberculosis (XDR-TB). Many patients have not achieved better clinical improvement after bedaquiline is stopped at 24 wk. However, there is no recommendation or guideline on bedaquiline administration beyond 24 wk, which is an important consideration when balancing the benefit of prognosis for XDR-TB against the uncertain safety concerning the newer antibiotics.
CASE SUMMARY: This paper reported 2 patients with XDR-TB (a female of 58 years of age and a female of 18 years of age) who received bedaquiline for 36 wk, as local experience to be shared. The 2 cases had negative cultures after 24 wk of treatment, but lung imaging was still positive. After discussion among experts, the consensus was made to bedaquiline prolongation by another 12 wk. The 36-wk prolonged use of bedaquiline in both cases achieved a favorable response without increasing the risk of cardiac events or new safety signals.
CONCLUSION: Longer regimen, including 36-wk bedaquiline treatment, might be an option for patients with XDR-TB. More studies are needed to explore the effectiveness and safety of prolonged use of bedaquiline for 36 wk vs standard 24 wk in the treatment of multidrug-resistant/XDR-TB or to investigate further the biomarkers and criteria indicative for extension of bedaquline to facilitate clinical use of this novel drug.

DOI: 10.12998/wjcc.v9.i10.2326
PMCID: PMC8026830
PMID: 33869610

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

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

Eur J Clin Microbiol Infect Dis. 2021 Apr 1. doi: 10.1007/s10096-021-04236-z.

Online ahead of print.

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

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

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

33. Controlling the Drug Resistant TB Epidemic in India: Challenges & Implications.

Epidemiol Health. 2021 Apr 7:e2021022. doi: 10.4178/epih.e2021022. Online ahead of print.

Husain AA(1), Kupz A(2), Kashyap RS(1).

India is highest Tuberculosis (TB) burden country accounting for an estimated one-fourth of the global burden. Drug resistant TB (DR-TB) represents major public health problem in India. Patients with DR-TB may often require profound changes in their drug regimen which are invariably linked to poor adherence and sub-optimal treatment outcomes compared to drug sensitive TB. The challenge of

addressing DR-TB is critical for India, as it accounts for over 27% of the global DR cases. In recent decade, India has been upfront in its battle against TB and even set up revised National Strategic plan (NSP) to eliminate TB by 2025. However, to achieve this ambitious goal, country will need multifaceted approach with respect to management of DR-TB. Despite concerted efforts driven by National TB elimination program, India faces substantial challenges with respect to DR-TB care especially in peripheral and resource limited endemic zones. The current article, describes some of the major challenges along with its implications associated with reducing the growing DR-TB epidemic in India.

DOI: 10.4178/epih.e2021022
PMID: 33831293

34. Greenness exposure and all-cause mortality during multi-drug resistant tuberculosis treatment: A population-based cohort study.

Sci Total Environ. 2021 Jun 1;771:145422. doi: 10.1016/j.scitotenv.2021.145422. Epub 2021 Jan 26.

Ge E(1), Gao J(2), Ren Z(3), Liu X(4), Luo M(5), Zhong J(6), Fei F(7), Chen B(8), Wang X(9), Wei X(10), Peng Y(11).

BACKGROUND: Living closer to greenness were thought to benefit various health outcomes. We aimed to assess the association between residential greenness and mortality among patients undergoing multidrug resistant tuberculosis (MDR-TB) treatment.
METHODS: We enrolled all local MDR-TB patients reported in Zhejiang, China from 2009 to 2017 and followed them throughout the treatment. We calculated the contemporaneous normalized difference vegetation index (NDVI) in the 250 and 500 m radius around patient's residence. Cox proportional hazards regression models with time-varying NDVI were used to assess the impact of greenness exposure on all-cause mortality during MDR-TB treatment, adjusting for potential individual and contextual covariates.
RESULTS: We ascertained 1,621 active MDR-TB cases, which contributed 3036 person-years at risk with an average follow-up of 684 days (s.d. 149 days) per patient. Among them, there were 163 deaths during follow-up, representing a crude mortality rate of 537 deaths per 10,000 person-years. Patients exposed to the second quintile (Q2) of greenness within the 500 m buffer had around 64% reduced mortality risk over the lowest quintile of greenness with hazard ratio (HR) = 0.364 (95% CI: 0.109-1.22). In lower nighttime light (NTL) areas, the hazard ratios (HR) per quintile increase in NDVI within the 500 m buffer were Q2: 0.35 (95% CI: 0.10-1.18), Q3: 0.24 (95% CI: 0.09-0.66), Q4: 0.26 (95% CI: 0.10-0.69), and Q5: 0.26 (95% CI: 0.10-0.71) relevant to the lowest quintile Q1,

with a trend of p-value ≤0.01. Patients who were female, younger (<60 years), resided in urban areas, or had high PM2.5 (i.e. particles with diagram ≤2.5 μm) exposure were more likely to benefit from greenness exposure. Associations were neither observed with NDVI in the 250 m buffer nor for patients living in higher NTL areas. There was a non-linear exposure-response relationship between greenness and deaths with p-value ≤0.05.
CONCLUSION: Increasing greenness exposure along with medical treatment reduces all-cause mortality among patients living in lower NTL areas.

DOI: 10.1016/j.scitotenv.2021.145422
PMID: 33548711 [Indexed for MEDLINE]

35. [Patient- and provider-related factors in the success of multidrug tuberculosis treatment in ColombiaFatores de êxito do tratamento da tuberculose multirresistente relacionados com o paciente e com a equipe de saúde na Colômbia].

Rev Panam Salud Publica. 2021 Apr 6;45:e5. doi: 10.26633/RPSP.2021.5. eCollection 2021.

[Article in Spanish]

Puerto Castro GM(1), Montes Zuluaga FN(2), Alcalde-Rabanal JE(3), Pérez F(4).

OBJECTIVE: To identify patient- and provider-related factors associated with the success of multidrug-resistant tuberculosis (MDR-TB) treatment in the six municipalities of Colombia with the highest number of MDR-TB cases.
METHODS: Bivariate and multivariate logistic regressions were used to analyze the association between treatment success (cure or treatment completion) and characteristics of the patients and physicians, nursing professionals, and psychologists involved in their treatment. The importance of knowledge in the management of MDR-TB cases was explored through focus groups with these providers.
RESULTS: Of 128 cases of TB-MDR, 63 (49.2%) experienced treatment success. Only 52.9% of the physicians and nursing professionals had satisfactory knowledge about MDR-TB. Logistic regression showed that being HIV negative, being affiliated with the contributory health insurance scheme, being cared for by a male physician, and being cared for by nursing professionals with sufficient knowledge were associated with a successful treatment outcome (p ≤ 0.05). Qualitative analysis showed the need for in-depth, systematic training of health

personnel who care for patients with MDR-TB.
CONCLUSIONS: Some characteristics of patients and healthcare providers influence treatment success in MDR-TB cases. Physicians' and nurses' knowledge about MDR-TB must be improved, and follow-up of MDR-TB patients who are living with HIV and of those affiliated with the subsidized health insurance scheme in Colombia must be strengthened, as these patients have a lower likelihood of a successful treatment outcome.

DOI: 10.26633/RPSP.2021.5
PMCID: PMC8021208
PMID: 33833785

36. In Silico Approach for Phytocompound-Based Drug Designing to Fight Efflux Pump-Mediated Multidrug-Resistant Mycobacterium tuberculosis.

Appl Biochem Biotechnol. 2021 Apr 7:1-23. doi: 10.1007/s12010-021-03557-1. Online ahead of print.

Biswas SS(1), Browne RB(2), Borah VV(2), Roy JD(2).

Tuberculosis (TB), caused by the bacteria Mycobacterium tuberculosis, is one of the principal causes of death in the world despite the existence of a significant number of antibiotics aimed against it. This is mainly due to the drug resistance mechanisms present in the bacterium, which leads to multidrug-resistant tuberculosis (MDR-TB). Additionally, the development of new antibiotics has become limited over the years. Although there are various drug resistance mechanisms present, efflux pumps are of utmost importance because they extrude out several dissimilar antitubercular drugs out of the cell. There are many efflux pump proteins present in Mycobacterium tuberculosis. Therefore, blocking these efflux pumps by inhibitors can raise the efficacy of the existing antibiotics and may also pave the path for the discovery and synthesis of new drugs. Plant compounds can act as a resource for the development of efflux pump inhibitors (EPIs), which may eventually replace or augment the current therapeutic options. This is mainly because plants have been traditionally used for ages for food or treatment and are considered safe with little or no side effects. Various computational tools are available which are used for the virtual screening of a large number of phytocompounds within a short span of time. This review aims to highlight the mechanism and appearance of drug resistance in Mycobacterium tuberculosis with emphasis on efflux pumps along with the significance of phytochemicals as inhibitors of these pumps and their screening strategy by computational approaches.

DOI: 10.1007/s12010-021-03557-1

PMCID: PMC8024441
PMID: 33826064

37. In vitro potency of 2-(((2-hydroxyphenyl)amino) methylene)-5,5-dimethylcyclohexane-1,3-dione against drug-resistant and nonreplicating persisters of Mycobacterium tuberculosis.

J Glob Antimicrob Resist. 2021 Mar 28:S2213-7165(21)00081-3. doi: 10.1016/j.jgar.2021.03.015. Online ahead of print.

Rather MA(1), Bhat ZS(2), Lone AM(3), Maqbool M(1), Bhat BA(3), Ahmad Z(4).

OBJECTIVES: New antituberculosis agents active on drug-resistant and nonreplicating tubercle bacilli remain an unmet medical obligation. We, therefore, evaluated a previously identified hit 2-(((2-hydroxyphenyl)amino) methylene)-5,5-dimethylcyclohexane-1,3-dione (PAMCHD) against a panel of clinical Mycobacterium tuberculosis isolates including multidrug-resistant (MDR) strains and against nonreplicating drug-tolerant persisters of M. tuberculosis H37Rv.
METHODS: potential against drug-resistant isolates of M.tuberculosis was investigated by broth dilution assay. CFU enumeration was done to determine the activity of PAMCHD against five kinds of dormant bacilli.
RESULTS: No significant difference in MICs of PAMCHD was observed against M .tuberculosis H37Rv (2.5-5 μg/mL) and eight drug-susceptible strains (1.25-5 μg/mL) as well as drug-resistant strains including six isoniazid (INH)- (2.5-10 μg/mL) one INH+ ethambutol (EMB)- (5 μg/mL), one RIF+ EMB- (5 μg/mL) resistant strains and three MDR strains. (2.5-10 μg/mL). Thereby, PAMCHD maintains its activity against all the kinds of clinical strains, especially against MDR strains. With respect to drug-tolerant persisters, INH and RIF killed 0.5 and 5.0 log10 CFUs of nonreplicating persisters developed by hypoxia and 1.5 and 2.5 log10 CFUs developed by nutrient starvation respectively at 64X of their respective MIC against actively dividing cultures. Contrary to this, PAMCHD sterilized persister cultures developed by hypoxia (killed 6.5 log10 CFU) or starvation (killed 7.5 log10 CFU). PAMCHD sterilized RIF tolerant (with tolerance level up to 100μg/mL of RIF) 100-day old static persisters at 64X MIC while moxifloxacin (MOX) was able to kill only 1.0 log10 CFU of these persisters at 64X MIC corresponding to MXF.
CONCLUSION: PAMCHD offers significant potential against MDR-TB and exhibits notable potency against nonreplicating drug-tolerant M. tuberculosis persisters. These findings warrant further studies on PAMCHD for further TB drug development.

DOI: 10.1016/j.jgar.2021.03.015
PMID: 33789204

38. Tuberculosis: An Overview of the Immunogenic Response, Disease Progression, and Medicinal Chemistry Efforts in the Last Decade toward the Development of Potential Drugs for Extensively Drug-Resistant Tuberculosis Strains.

J Med Chem. 2021 Apr 7. doi: 10.1021/acs.jmedchem.0c01833. Online ahead of print.

Sharma A(1)(2), De Rosa M(3), Singla N(1), Singh G(2), Barnwal RP(1), Pandey A(4).

Tuberculosis (TB) is a slow growing, potentially debilitating disease that has plagued humanity for centuries and has claimed numerous lives across the globe. Concerted efforts by researchers have culminated in the development of various strategies to combat this malady. This review aims to raise awareness of the rapidly increasing incidences of multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis, highlighting the significant modifications that were introduced in the TB treatment regimen over the past decade. A description of the role of pathogen-host immune mechanisms together with strategies for prevention of the disease is discussed. The struggle to develop novel drug therapies has continued in an effort to reduce the treatment duration, improve patient compliance and outcomes, and circumvent TB resistance mechanisms. Herein, we give an overview of the extensive medicinal chemistry efforts made during the past decade toward the discovery of new chemotypes, which are potentially active against TB-resistant strains.

DOI: 10.1021/acs.jmedchem.0c01833
PMID: 33826327

39. Risk factors for mortality among patients diagnosed with multi-drug resistant tuberculosis in Uganda- a case-control study.

BMC Infect Dis. 2021 Mar 22;21(1):292. doi: 10.1186/s12879-021-05967-2.

Kizito E(1), Musaazi J(2), Mutesasira K(1), Twinomugisha F(1), Namwanje H(1), Kiyemba T(1), Freitas Lopez DB(3), Nicholas NS(1), Nkolo A(1), Birabwa E(4), Dejene S(4), Zawedde-Muyanja S(5)(6).

BACKGROUND: The World Health Organization (WHO) End TB strategy aims to reduce mortality due to tuberculosis (TB) to less than 5% by 2035. However, mortality

due to multidrug-resistant tuberculosis (MDR-TB) remains particularly high. Globally, almost 20% of patients started on MDR-TB treatment die during the course of treatment every year. We set out to examine the risk factors for mortality among a cohort of patients diagnosed with MDR-TB in Uganda.
METHODS: We conducted a case-control study nested within the national MDR-TB cohort. We defined cases as patients who died from any cause during the course of MDR-TB treatment. We selected two controls for each case from patients alive and on MDR-TB treatment at the time that the death occurred (incidence-density sampling). We matched the cases and controls on health facility at which they were receiving care. We performed conditional logistic regression to identify the risk factors for mortality.
RESULTS: Data from 198 patients (66 cases and 132 controls) started on MDR-TB treatment from January 1 to December 31, 2016, was analyzed for this study. Cases were similar to controls in age/sex distribution, occupation and history of TB treatment. However, cases were more likely to be HIV infected while controls were more likely to have attained secondary level education. On multivariate regression analysis, co-infection with HIV (aOR 1.9, 95% CI [1.1-4.92] p = 0.05); non-adherence to MDR-TB treatment (aOR 1.92, 95% CI [1.02-4.83] p = 0.04); age over 50 years (aOR 3.04, 95% CI [1.13-8.20] p = 0.03); and having no education (aOR 3.61, 95% CI [1.1-10.4] p = 0.03) were associated with MDR-TB mortality.
CONCLUSION: To mitigate MDR-TB mortality, attention must be paid to provision of social support particularly for older persons on MDR-TB treatment. In addition, interventions that support treatment adherence and promote early detection and management of TB among HIV infected persons should also be emphasized.

DOI: 10.1186/s12879-021-05967-2
PMCID: PMC7986038
PMID: 33752637 [Indexed for MEDLINE]

40. Unfavorable Treatment Outcome and Its Predictors Among Patients with Multidrug-Resistance Tuberculosis in Southern Ethiopia in 2014 to 2019: A Multi-Center Retrospective Follow-Up Study.

Infect Drug Resist. 2021 Apr 8;14:1343-1355. doi: 10.2147/IDR.S300814. eCollection 2021.

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

BACKGROUND: According to the 2017 global report, Ethiopia is among the top 30 high tuberculosis (TB) and multidrug-resistant tuberculosis (MDR-TB) burden countries. However, studies on MDR-TB treatment outcomes in Southern Ethiopia was very limited. Therefore, the study was aimed at determining the unfavorable

treatment outcome and its predictors among patients with multidrug-resistant tuberculosis in Southern Ethiopia MDR-TB treatment centers.
SUBJECTS AND METHODS: A retrospective follow-up study was conducted in Southern Ethiopia MDR-TB treatment initiating centers. Three hundred sixty-three patients were included in the study. Kaplan-Meier failure curve, median time, and Log rank test were used to present the descriptive findings. Then, a Cox regression analysis was used to identify predictors of unfavorable treatment outcome. The strength of the association was reported using an adjusted hazard ratio (AHR) and a 95% confidence interval (CI). Finally, the Cox Snell residual test was used to check the goodness of fit.
RESULTS: For the entire cohort, the unfavorable treatment outcome was 23.68% (19.29, 28.09). Hospitalization for care (AHR = 2.07; 95% CI = 1.21, 3.63), male sex (AHR = 1.85; 95% CI = 1.002, 3.42), attending tertiary education (AHR = 0.31; 95% CI = 0.11, 0.91), and those with low hemoglobin (AHR = 2.89; 95% CI = 1.55, 5.38) were predictors for unfavorable treatment outcome.
CONCLUSION: The unfavorable treatment outcome was higher compared with the national goal of END-TB by 2020. Hospitalizations for care, male sex, and low hemoglobin level increased the hazard of the unfavorable treatment outcome. On the other hand, attending territory education decreased the hazard of the unfavorable treatment outcome.

DOI: 10.2147/IDR.S300814
PMCID: PMC8041603
PMID: 33854347

41. Dr PK Sen TAI gold medal oration.

Indian J Tuberc. 2021 Apr;68(2):307-310. doi: 10.1016/j.ijtb.2021.02.008. Epub 2021 Feb 8.

Singla R(1).

The current write-up is for Dr P.K.Sen TAI Gold Medal Oration Award for 2020 conferred to Dr Rupak Singla and delivered on 19 th December 2020. The title chosen for the oration was "Introduction and scale up of new anti-TB drugs in India: role of NITRD." However, in the oration the role this institute has played for overall scale up of Drug-resistant TB services in India under National Tuberculosis Elimination Programme (NTEP) at different times from the beginning of national TB programme has also been presented. National Institute of TB and Respiratory Diseases has travelled with our country from beginning of DR-TB care. It demonstrated for the first time use of a Standardized Treatment

Regimen with second line drugs for MDR-TB in field conditions. NITRD assisted NTEP for the concept of DST guided treatment. This institute guided NTEP for the management of MDR-TB failure patients with Pre-XDR and XDR-TB. Also, NITRD assisted India for the introduction of newer DR-TB drugs and scale up of newer drugs across the country. The strength of NITRD include clinical expertise, laboratory support and training division. NITRD commitment is strong and will continue to support NTEP for all endeavors in future also.

DOI: 10.1016/j.ijtb.2021.02.008
PMID: 33845973

42. New definitions of pre-extensively and extensively drug-resistant tuberculosis: update from the World Health Organization.

Eur Respir J. 2021 Apr 8;57(4):2100361. doi: 10.1183/13993003.00361-2021. Print 2021 Apr.

Viney K(1), Linh NN(1), Gegia M(1), Zignol M(1), Glaziou P(1), Ismail N(1), Kasaeva T(1), Mirzayev F(1).

DOI: 10.1183/13993003.00361-2021
PMID: 33833074

43. Comprehensive review on mechanism of action, resistance and evolution of antimycobacterial drugs.

Life Sci. 2021 Jun 1;274:119301. doi: 10.1016/j.lfs.2021.119301. Epub 2021 Mar 3.

Chauhan A(1), Kumar M(2), Kumar A(3), Kanchan K(4).

Tuberculosis is one of the deadliest infectious diseases existing in the world since ancient times and still possesses serious threat across the globe. Each year the number of cases increases due to high drug resistance shown by Mycobacterium tuberculosis (Mtb). Available antimycobacterial drugs have been classified as First line, Second line and Third line antibiotics depending on the time of their discoveries and their effectiveness in the treatment. These antibiotics have a broad range of targets ranging from cell wall to metabolic processes and their non-judicious and uncontrolled usage in the treatment for years has created a significant problem called multi-drug resistant (MDR)

tuberculosis. In this review, we have summarized the mechanism of action of all the classified antibiotics currently in use along with the resistance mechanisms acquired by Mtb. We have focused on the new drug candidates/repurposed drugs, and drug in combinations, which are in clinical trials for either treating the MDR tuberculosis more effectively or involved in reducing the time required for the chemotherapy of drug sensitive TB. This information is not discussed very adequately on a single platform. Additionally, we have discussed the recent technologies that are being used to discover novel resistance mechanisms acquired by Mtb and for exploring novel drugs. The story of intrinsic resistance mechanisms and evolution in Mtb is far from complete. Therefore, we have also discussed intrinsic resistance mechanisms of Mtb and their evolution with time, emphasizing the hope for the development of novel antimycobacterial drugs for effective therapy of tuberculosis.

DOI: 10.1016/j.lfs.2021.119301
PMID: 33675895 [Indexed for MEDLINE]

44. Increasing prevalence of resistance to second-line drugs among multidrug-resistant Mycobacterium tuberculosis isolates in Kuwait.

Sci Rep. 2021 Apr 8;11(1):7765. doi: 10.1038/s41598-021-87516-0.

Al-Mutairi NM(1), Ahmad S(2), Mokaddas E(1)(3).

Molecular methods detect genetic mutations associated with drug resistance. This study detected resistance-conferring mutations in gyrA/gyrB for fluoroquinolones and rrs/eis genes for second-line injectable drugs (SLIDs) among multidrug-resistant Mycobacterium tuberculosis (MDR-TB) isolates in Kuwait. Fifty pansusceptible M. tuberculosis and 102 MDR-TB strains were tested. Phenotypic susceptibility testing was performed by MGIT 960 system using SIRE drug kit. GenoType MTBDRsl version 1 (gMTBDRslv1) and GenoType MTBDRsl version 2 (gMTBDRslv2) tests were used for mutation detection. Results were validated by PCR-sequencing of respective genes. Fingerprinting was performed by spoligotyping. No mutations were detected in pansusceptible isolates. gMTBDRslv1 detected gyrA mutations in 12 and rrs mutations in 8 MDR-TB isolates. gMTBDRsl2 additionally detected gyrB mutations in 2 and eis mutation in 1 isolate. Mutations in both gyrA/gyrB and rrs/eis were not detected. gMTBDRslv1 also detected ethambutol resistance-conferring embB mutations in 59 isolates. Although XDR-TB was not detected, frequency of resistance-conferring mutations for fluoroquinolones or SLIDs was significantly higher among isolates collected during 2013-2019 versus 2006-2012. Application of both tests is warranted for

proper management of MDR-TB patients in Kuwait as gMTBDRslv2 detected resistance to fluoroquinolones and/or SLIDs in 3 additional isolates while gMTBDRslv1 additionally detected resistance to ethambutol in 58% of MDR-TB isolates.

DOI: 10.1038/s41598-021-87516-0
PMCID: PMC8032671
PMID: 33833390

45. Sorry for the delay.

Clin Microbiol Infect. 2021 Apr 3:S1198-743X(21)00142-7. doi: 10.1016/j.cmi.2021.03.007. Online ahead of print.

Lange C(1), Chesov D(2), Konstatynovska O(3), Mandalakas AM(4), Udwadia Z(5).

Patients affected by tuberculosis should be adequately treated. Those who are diagnosed early in the course of the disease have a better chance for a successful outcome than patients where the diagnosis of tuberculosis is delayed. We have been invited to comment on an article accepted for publication in CMI that addresses delays in the diagnosis of tuberculosis in China and we are discussing different mechanisms leading to delayed or inadequate tuberculosis treatments.

DOI: 10.1016/j.cmi.2021.03.007
PMID: 33823271

46. Potent anti-mycobacterial and immunomodulatory activity of some bioactive molecules of Indian ethnomedicinal plants that have the potential to enter in TB management.

J Appl Microbiol. 2021 Mar 26. doi: 10.1111/jam.15088. Online ahead of print.

Sarangi A(1), Das BS(1), Patnaik G(2), Sarkar S(3), Debnath M(4), Mohan M(5), Bhattacharya D(1).

Tuberculosis (TB) is one of the deadliest infectious diseases of human civilization. Approximately one-third of global population is latently infected with the TB pathogen Mycobacterium tuberculosis (M.tb). The discovery of anti-TB antibiotics leads to decline in death rate of TB. However, the evolution of antibiotic-resistant M.tb-strain and the resurgence of different

immune-compromised diseases re-escalated the death rate of TB. WHO has already cautioned about the chances of pandemic situation in TB endemic countries until the discovery of new anti-tubercular drugs, that is, the need of the hour. Analysing the pathogenesis of TB, it was found that M.tb evades the host by altering the balance of immune response and affects either by killing the cells or by creating inflammation. In the pre-antibiotic era, traditional medicines were only therapeutic measures for different infectious diseases including tuberculosis. The ancient literatures of India or ample Indian traditional knowledge and ethnomedicinal practices are evidence for the treatment of TB using different indigenous plants. However, in the light of modern scientific approach, anti-TB effects of those plants and their bioactive molecules were not established thoroughly. In this review, focus has been given on five bioactive molecules of different traditionally used Indian ethnomedicinal plants for treatment of TB or TB-like symptom. These compounds are also validated with proper identification and their mode of action with modern scientific approaches. The effectiveness of these molecules for sensitive or drug-resistant TB pathogen in clinical or preclinical studies was also evaluated. Thus, our specific aim is to highlight such scientifically validated bioactive compounds having anti-mycobacterial and immunomodulatory activity for future use as medicine or adjunct-therapeutic molecule for TB management.

DOI: 10.1111/jam.15088
PMID: 33772980

47. Assessment of burden of drug-resistant tuberculosis at a tertiary care centre in northern India: a prospective single centre cohort study.

BMJ Open. 2021 Apr 15;11(4):e044096. doi: 10.1136/bmjopen-2020-044096.

Misra R(1), Kesarwani V(1), Nath A(2).

OBJECTIVES: We aim to define the burden of rifampicin monoresistant tuberculosis (TB) at a tertiary care centre in northern India as well as determine the second-line drug susceptibilities (SL-DST) in a subset of patients.
METHODS: A total of 3045 pulmonary (n=1883) and extrapulmonary (n=1162) samples from likely patients with TB were subjected to microscopy, culture and the Xpert MTB/RIF assay from March 2017 to June 2019. SL-DST testing by line probe assay version 2 for fluoroquinolones (FQs) and second-line injectable drugs were performed on 62 samples.
RESULTS: Out of 3045 samples processed in our laboratory during the study period, 36.1% (1101/3045) were positive for Mycobacterium tuberculosis complex

(MTBC) and 21.6% were rifampicin monoresistant (223/1032). The rate of rifampicin resistance in pulmonary samples was 23.5% (166/706) and in extrapulmonary cases, it was 17.4% (57/326). Out of 62 cases included for second-line testing, 48 were resistant to FQs (77.4%) while 11 were extensively drug resistant.
CONCLUSIONS: India urgently needs to arrest an emerging multidrug-resistant TB epidemic with associated resistance to FQs. A robust surveillance system is needed to execute the National Strategic Plan for 2017-2025.

DOI: 10.1136/bmjopen-2020-044096
PMID: 33858870

48. Isoniazid-monoresistant tuberculosis in France: risk factors, treatment outcomes and adverse events.

Int J Infect Dis. 2021 Apr 3:S1201-9712(21)00311-8. doi: 10.1016/j.ijid.2021.03.093. Online ahead of print.

Bachir M(1), Guglielmetti L(2), Tunesi S(3), Billard-Pomares T(4), Chiesi S(5), Jaffré J(6), Langris H(7), Pourcher V(8), Schramm F(9), Lemaître N(10), Robert J(2); Isoniazid Resistance Group.

OBJECTIVES: Isoniazid-monoresistant tuberculosis (HR-TB) is the most prevalent form of drug-resistant TB worldwide and in France and is associated with poorer treatment outcomes compared to drug-susceptible TB (DS-TB). The objective of this study was to determine the characteristics of HR-TB patients in France and to compare outcomes and safety of treatment for HR-TB and DS-TB.
METHODS: A case-control multicentre study was performed to identify risk factors associated with HR-TB and to compare treatment outcomes and safety among HR-TB patients and DS-TB patients.
RESULTS: Characteristics of 99 HR-TB diagnosed and treated in university hospitals of Paris, Lille, Caen and Strasbourg were compared to 99 DS-TB's. Female sex (OR = 2.2; 1.0-4.7), birth in the West-Pacific WHO region (OR = 4.6; 1.1-18.7) and resistance to streptomycin (OR = 77.5; 10.1-594.4) were found to be independently associated with HR-TB. Rates of treatment success did not differ significantly between HR-TB and DS-TB.
CONCLUSIONS: Factors associated with HR-TB are not relevant enough to efficiently screen TB patients at risk of HR-TB. The systematic implementation of rapid molecular testing on clinical samples remains the only effective way to make the early diagnosis of HR-TB and adapt the treatment.

DOI: 10.1016/j.ijid.2021.03.093
PMID: 33823278

49. Tuberculosis among Migrant Populations in Sicily: A Field Report.

J Trop Med. 2021 Mar 30;2021:7856347. doi: 10.1155/2021/7856347. eCollection 2021.

Prestileo T(1)(2), Pipitone G(1)(3), Sanfilippo A(1), Ficalora A(1), Natoli G(4), Corrao S(4)(5), Team I Ta C A Immigrant Take Care Advocacy Team(6).

BACKGROUND: In the EU, tuberculosis (TB) mainly affects vulnerable people, including migrants. From 2014 to 2017, we have estimated the frequency of both tuberculosis and latent tuberculosis infection (LTBI) among the migrant population hosted in 41 reception centers in western Sicily (ITaCA network).
MATERIALS AND METHODS: All migrants were consecutively recruited for the screening of TB infection with physical examination and TST in 1,020 migrants and with IGRA in the others 2,690. The screening was carried out 4-8 weeks after landing in Sicily. For all migrants with a positive screening test, chest X-ray and smear examination were performed. LTBI was defined by positivity of TST or IGRA with negative X-ray chest, clinical, and smear examination. Active TB was defined by radiological and/or clinical and/or sputum positivity in a patient with a TST or IGRA positivity.
RESULTS: We evaluated a total of 3,710 migrants, of which 89% came from Sub-Saharan countries; 2,811 were males, 899 were females, with a median age of 22 years (IQR: 18-25). TB infection was diagnosed in 501 persons (13.5%) of which 440 (11.8%) had LTBI and 61 had active TB (1.6%): 1 had lymph node TB, 1 had intestinal TB, and 59 had pulmonary TB (38 sputum smear positive TB; no drug-resistant TB were observed).
CONCLUSIONS: TB screening is critical to early diagnosis and treatment.

DOI: 10.1155/2021/7856347
PMCID: PMC8024091
PMID: 33859702

50. Identification of active molecules against Mycobacterium tuberculosis through machine learning.

Brief Bioinform. 2021 Apr 5:bbab068. doi: 10.1093/bib/bbab068. Online ahead of print.

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

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

DOI: 10.1093/bib/bbab068
PMID: 33822874

51. TB research and innovation in Latin America.

Eur Respir Rev. 2021 Mar 24;30(159):200107. doi: 10.1183/16000617.0107-2020. Print 2021 Mar 31.

Manga S(1).

The production of tuberculosis (TB) research and innovation in Latin America during the past decade has notably improved. Its role in the acceleration of the

decline of the average annual TB incidence rate by 2.5% from 2017 to 2018 is still unclear, but it is looking promising that the region will meet the End TB Strategy targets set for 2030. Well performed and high-quality research and evidence is critical for improving national TB control programme outcomes. In Latin America, this need is most apparent when responding to the multidrug-resistant TB epidemic.There is an urgent need for technological breakthroughs to accelerate by an average of 17% per year if the decline in TB incidence rate is to meet the target set for 2030. Intensified research and innovation, identified as one of the three essential pillars of the End TB Strategy, has scarcely been achieved in the region due to political and economic context. This will be analysed further in this article.

DOI: 10.1183/16000617.0107-2020
PMID: 33762425

52. Factors Influencing Adherence to Tuberculosis Treatment in the Ketu North District of the Volta Region, Ghana.

Tuberc Res Treat. 2021 Mar 30;2021:6685039. doi: 10.1155/2021/6685039. eCollection 2021.

Dogah E(1), Aviisah M(2), Kuatewo DM(3), Kpene GE(4), Lokpo SY(4), Edziah FS(4).

Annually, ten million cases of tuberculosis (TB) and about 1.8 million mortalities are recorded. Adherence to TB treatment not only reduces death outcomes but prevents prolonged sickness, transmission to others, and the development of multidrug-resistant TB. This study is aimed at determining the rate of treatment adherence, knowledge of TB infection, and the possible factors influencing adherence to TB treatment in the Ketu North District in the Volta Region of Ghana. A cross-sectional study design was employed. A semistructured questionnaire was used to obtain data from respondents. Adherence to TB treatment and knowledge level about TB infection were assessed. A Chi-square test analysis was used to determine the variables that were associated with treatment adherence. Logistic regression analysis was used to determine potential factors that contribute to treatment adherence. A total of 125 TB registrants were enrolled in the study. The majority (102 (81.6%)) adhered to the TB treatment regimen. However, the level of knowledge about night sweat being a symptom of TB infection was relatively low (78 (62.4%)). Logistic regression analysis revealed that the male gender was about three times more likely (OR = 2.978, 95%CI = 1.173-7.561; p = 0.022) to be associated with adherence to TB treatment. However, food availability (OR = 2.208, 95% CI

(0.848-5.753); p = 0.10) and household size (OR = 0.538, 95% CI (0.195-1.483); p = 0.23) were not significantly associated with treatment adherence. In this study, adherence to TB treatment and the knowledge level of TB infection were high. However, the knowledge level of night sweat being a symptom of TB infection was relatively low. Being a male was significantly associated with treatment adherence. An intensified health education on the symptoms of TB infection is therefore recommended.

DOI: 10.1155/2021/6685039
PMCID: PMC8026325
PMID: 33859843

53. Therapeutic drug monitoring and fluoroquinolones for multidrug-resistant tuberculosis.

Eur Respir J. 2021 Apr 1;57(4):2004454. doi: 10.1183/13993003.04454-2020. Print 2021 Apr.

Srivastava S(1)(2), Gumbo T(3).

Comment on
Eur Respir J. 2021 Mar 11;57(3):

DOI: 10.1183/13993003.04454-2020
PMID: 33795358

54. Uptake of universal drug susceptibility testing among people with TB in a south Indian district: How are we faring?

Trans R Soc Trop Med Hyg. 2021 Apr 6:trab051. doi: 10.1093/trstmh/trab051. Online ahead of print.

Ranganath R(1), Shewade HD(2)(3), Bahadur AK(1), Naik V(1), Nagaraja SB(4), Kumar AMV(2)(3)(5), Peerapur BV(1), Babu S(6), Somshekhar N(7), Singarajipur A(8).

BACKGROUND: India implements universal drug susceptibility testing (UDST) using rapid genotypic tests (cartridge-based nucleic acid amplification test CBNAAT - and line probe assay - LPA). to bridge the gap of diagnosis of multidrug/rifampicin-resistant TB. There is limited evidence assessing the

implementation of UDST in India. We assessed the implementation among people with pulmonary TB notified from public facilities in October 2019 from Raichur (Karnataka), India.
METHODS: A cohort study involving secondary data in routine programme settings was conducted. All people with TB underwent a rapid genotypic DST for rifampicin resistance followed by first line-LPA (FL-LPA) if sensitive and second line-LPA (SL-LPA) if resistant.
RESULTS: Of 217 people, 15.7% (n=34) did not undergo rapid genotypic DST. Of 135 who were rifampicin-sensitive detected on CBNAAT, 68.1% (n=92) underwent FL-LPA, and out of the six rifampicin-resistant cases, 66.7% (n=4) underwent SL-LPA. Overall, 65.4% (142/217) completed the UDST algorithm. Children (aged <15 y) and people with bacteriological non-confirmation on microscopy were less likely to undergo rapid genotypic DST. Of 183 patients who underwent both rapid genotypic DST and sputum smear microscopy, 150 were bacteriologically confirmed and, of them, 9 (6%) were 'rapid DST-negative'.
CONCLUSION: We found gaps at various steps. There were a significant number of 'rapid DST-negative, smear-positive' patients.

DOI: 10.1093/trstmh/trab051
PMID: 33823556

55. Optimizing Bedaquiline for cardiotoxicity by structure based virtual screening, DFT analysis and molecular dynamic simulation studies to identify selective MDR-TB inhibitors.

In Silico Pharmacol. 2021 Mar 23;9(1):23. doi: 10.1007/s40203-021-00086-x. eCollection 2021.

Ahmad I(1), Jadhav H(1), Shinde Y(1), Jagtap V(1), Girase R(1), Patel H(1).

Since the last 4 decades, Bedaquiline has been the first drug discovered as a new kind of anti-tubercular agent and received FDA approval in December 2012 to treat pulmonary multi-drug resistance tuberculosis (MDR-TB). It demonstrates excellent efficacy against MDR-TB by effectively inhibiting mycobacterial ATP synthase. In addition to these apparent assets of Bedaquiline, potential disadvantages of Bedaquiline include inhibition of the hERG (human Ether-à-go-related gene; KCNH2), potassium channel (concurrent risk of cardiac toxicity), and risk of phospholipidosis due to its more lipophilic nature. To assist the effective treatment of MDR-TB, highly active Bedaquiline analogs that display a better safety profile are urgently needed. A structure-based virtual

screening approach was used to address the toxicity problems associated with Bedaquiline. Among the virtually screened compound, CID 15947587 had significant docking affinity (- 5.636 kcal/mol) and highest binding free energy (ΔG bind - 85.2703 kcal/mol) towards the Mycobacterial ATP synthase enzyme with insignificant cardiotoxicity and lipophilicity. During MD simulation studies (50 ns), the molecule optimizes its conformation to fit better the active receptor site justifying the binding affinity. The obtained results showed that CID15947587 could be a useful template for further optimizing the MDR-TB inhibitor.
SUPPLEMENTARY INFORMATION: The online version contains supplementary material available at 10.1007/s40203-021-00086-x.

DOI: 10.1007/s40203-021-00086-x
PMCID: PMC7988025
PMID: 33854869

56. Molecular epidemiology of Mycobacterium tuberculosis in adult Filipino TB-HIV co-infected patients.

Int J Tuberc Lung Dis. 2021 Apr 1;25(4):285-291. doi: 10.5588/ijtld.20.0878.

Malabad JCM(1), Ang CF(1), Palabrica FAR(1), Cajucom MAM(1), Gloriani NG(2), Villanueva SYAM(2), Montoya JC(1).

BACKGROUND: TB is the leading cause of death from a single infectious disease, particularly among people living with HIV (PLHIV). Molecular epidemiology provides information on prevalent genotypes of Mycobacterium tuberculosis and disease transmission dynamics, which aid in TB control. Identification of mutations that confer drug resistance is essential for the rapid diagnosis of drug-resistant TB, especially in high TB burden settings, like the Philippines.METHODS: This study aimed to determine mutations in M. tuberculosis drug resistance-conferring genes and circulating genotypes in PLHIV. MIRU-VNTR (mycobacterial interspersed repetitive unit-variable number of tandem repeats) typing using a set of 24-loci and sequencing of drug resistance-conferring genes were performed in 22 M. tuberculosis isolates from TB-HIV co-infected patients.RESULTS: The prevalence of resistance to any drug was 31.8%, 18.2% for isoniazid monoresistance, 4.5% for streptomycin monoresistance and 9.1% for multidrug resistance. The identified mutations in the katG, rpoB, pncA, rpsL and gyrA genes have been reported in the literature; none was found in the inhA and embB genes. All isolates belonged to the EAI2-Manila family and were grouped

into four clusters based on their phenotypic drug resistance and mutation profiles.CONCLUSION: The use of 24-loci set may be used as a more discriminatory MIRU-VNTR typing in settings where the East African-Indian lineage is predominant, like the Philippines.

DOI: 10.5588/ijtld.20.0878
PMID: 33762072

57. Does Ghana's National Health Insurance Scheme provide financial protection to tuberculosis patients and their households?

Soc Sci Med. 2021 Mar 27;277:113875. doi: 10.1016/j.socscimed.2021.113875. Online ahead of print.

Pedrazzoli D(1), Carter DJ(2), Borghi J(3), Laokri S(4), Boccia D(2), Houben RM(5).

Financial barriers are a key limitation to accessing health services, such as tuberculosis (TB) care in resource-poor settings. In Ghana, the National Health Insurance Scheme (NHIS), established in 2003, officially offers free TB care to those enrolled. Using data from the first Ghana's national TB patient cost survey, we address two key questions 1) what are the key determinants of costs and affordability for TB-affected households, and 2) what would be the impact on costs for TB-affected households of expanding NHIS to all TB patients? We reported the level of direct and indirect costs, the proportion of TB-affected households experiencing catastrophic costs (defined as total TB-related costs, i.e., direct and indirect, exceeding 20% of their estimated pre-diagnosis annual household income), and potential determinants of costs, stratified by insurance status. Regression models were used to determine drivers of costs and affordability. The effect of enrolment into NHIS on costs was investigated through Inverse Probability of Treatment Weighting Analysis. Higher levels of education and income, a bigger household size and an multi-drug resistant TB diagnosis were associated with higher direct costs. Being in a low wealth quintile, living in an urban setting, losing one's job and having MDR-TB increased the odds of experiencing catastrophic costs. There was no evidence to suggest that enrolment in NHIS defrayed medical, non-medical, or total costs, nor mitigated income loss. Even if we expanded NHIS to all TB patients, the analyses suggest no evidence for any impact of insurance on medical cost, income loss, or total cost. An expansion of the NHIS programme will not relieve the financial burden for TB-affected households. Social protection schemes require enhancement if they are to protect TB patients from financial catastrophe.

DOI: 10.1016/j.socscimed.2021.113875
PMID: 33848718

58. Tuberculosis: A persistent unpleasant neighbour of humans.

J Infect Public Health. 2021 Apr;14(4):508-513. doi: 10.1016/j.jiph.2021.01.005. Epub 2021 Jan 11.

Seki M(1), Choi H(2), Kim K(3), Whang J(3), Sung J(4), Mitarai S(5).

Mycobacterium tuberculosis, the bacterium that causes tuberculosis, has long been an unpleasant neighbour of humans. Following transmission of the bacterium from patients with active infection, new hosts do not immediately develop symptoms, as M. tuberculosis initially remains quiescent. However, it is eventually triggered, leading to the infection of other individuals. Humans are the exclusive host, and the rapid proliferation of the human population worldwide along with increasing globalisation have contributed to the pathogen's persistence, as have the survival strategies employed by M. tuberculosis, especially its resistance to several antimicrobials. Defeating this enemy will require novel approaches.

DOI: 10.1016/j.jiph.2021.01.005
PMID: 33743373 [Indexed for MEDLINE]

60. Data quality assessment of a South African electronic registry for drug-resistant TB, 2015-2016.

Public Health Action. 2021 Mar 21;11(1):33-39. doi: 10.5588/pha.20.0031.

Manesen R(1), Mekler KA(1), Molobi TR(1), Tyiki AA(1), Madlavu MJ(2), Velen K(1), Charalambous S(1), van der Heijden YF(1)(3)(4).

SETTING: Assessment of bedaquiline roll-out in South Africa requires accurate patient data in EDRWeb, a national case-based rifampicin-resistant TB (RR-TB) surveillance register.
OBJECTIVE: To ensure EDRWeb data reflect programmatic DR-TB source data, we implemented a data quality improvement initiative.
DESIGN: We conducted data quality assessments of EDRWeb data compared to paper patient folders at two South African RR-TB treatment facilities in 2015 and

2016. We assessed 80 patient records before the intervention for completeness of clinically relevant data fields, and 80 different records after the intervention for completeness and concordance. The intervention involved reviewing and updating EDRWeb along with data quality audits with direct feedback to sites. RESULTS: At baseline data completeness per site was lowest for variables related to electrocardiogram (ECG) data, adverse events, and concomitant medications (completeness for these fields ranged from 0% to 80%). Post-intervention data completeness and concordance were high for all fields except those related to ECG data (ECG-related field completeness ranged from 10% to 100%). CONCLUSION: After a data quality initiative, data completeness improved at each site with the exception of ECG data fields. Our findings suggest that data quality interventions may improve patient clinical registries, ultimately enabling better evidence-based decision making for TB programmes.

DOI: 10.5588/pha.20.0031
PMCID: PMC7987250
PMID: 33777719

61. Validation of a host blood transcriptomic biomarker for pulmonary tuberculosis in people living with HIV: a prospective diagnostic and prognostic accuracy study.

Lancet Glob Health. 2021 Apr 13:S2214-109X(21)00045-0. doi: 10.1016/S2214-109X(21)00045-0. Online ahead of print.

Mendelsohn SC(1), Fiore-Gartland A(2), Penn-Nicholson A(1), Mulenga H(1), Mbandi SK(1), Borate B(2), Hadley K(1), Hikuam C(1), Musvosvi M(1), Bilek N(1), Erasmus M(1), Jaxa L(1), Raphela R(1), Nombida O(1), Kaskar M(1), Sumner T(3), White RG(3), Innes C(4), Brumskine W(4), Hiemstra A(5), Malherbe ST(5), Hassan-Moosa R(6), Tameris M(1), Walzl G(5), Naidoo K(6), Churchyard G(7), Scriba TJ(1), Hatherill M(8); CORTIS-HR Study Team.

BACKGROUND: A rapid, blood-based triage test that allows targeted investigation for tuberculosis at the point of care could shorten the time to tuberculosis treatment and reduce mortality. We aimed to test the performance of a host blood transcriptomic signature (RISK11) in diagnosing tuberculosis and predicting progression to active pulmonary disease (prognosis) in people with HIV in a community setting.
METHODS: In this prospective diagnostic and prognostic accuracy study, adults (aged 18-59 years) with HIV were recruited from five communities in South Africa. Individuals with a history of tuberculosis or household exposure to multidrug-resistant tuberculosis within the past 3 years, comorbid risk factors

for tuberculosis, or any condition that would interfere with the study were excluded. RISK11 status was assessed at baseline by real-time PCR; participants and study staff were masked to the result. Participants underwent active surveillance for microbiologically confirmed tuberculosis by providing spontaneously expectorated sputum samples at baseline, if symptomatic during 15 months of follow-up, and at 15 months (the end of the study). The coprimary outcomes were the prevalence and cumulative incidence of tuberculosis disease confirmed by a positive Xpert MTB/RIF, Xpert Ultra, or Mycobacteria Growth Indicator Tube culture, or a combination of such, on at least two separate sputum samples collected within any 30-day period.
FINDINGS: Between March 22, 2017, and May 15, 2018, 963 participants were assessed for eligibility and 861 were enrolled. Among 820 participants with valid RISK11 results, eight (1%) had prevalent tuberculosis at baseline: seven (2·5%; 95% CI 1·2-5·0) of 285 RISK11-positive participants and one (0·2%; 0·0-1·1) of 535 RISK11-negative participants. The relative risk (RR) of prevalent tuberculosis was 13·1 times (95% CI 2·1-81·6) greater in RISK11-positive participants than in RISK11-negative participants. RISK11 had a diagnostic area under the receiver operating characteristic curve (AUC) of 88·2% (95% CI 77·6-96·7), and a sensitivity of 87·5% (58·3-100·0) and specificity of 65·8% (62·5-69·0) at a predefined score threshold (60%). Of those with RISK11 results, eight had primary endpoint incident tuberculosis during 15 months of follow-up. Tuberculosis incidence was 2·5 per 100 person-years (95% CI 0·7-4·4) in the RISK11-positive group and 0·2 per 100 person-years (0·0-0·5) in the RISK11-negative group. The probability of primary endpoint incident tuberculosis was greater in the RISK11-positive group than in the RISK11-negative group (cumulative incidence ratio 16·0 [95% CI 2·0-129·5]). RISK11 had a prognostic AUC of 80·0% (95% CI 70·6-86·9), and a sensitivity of 88·6% (43·5-98·7) and a specificity of 68·9% (65·3-72·3) for incident tuberculosis at the 60% threshold.
INTERPRETATION: RISK11 identified prevalent tuberculosis and predicted risk of progression to incident tuberculosis within 15 months in ambulant people living with HIV. RISK11's performance approached, but did not meet, WHO's target product profile benchmarks for screening and prognostic tests for tuberculosis.
FUNDING: Bill & Melinda Gates Foundation and the South African Medical Research Council.

DOI: 10.1016/S2214-109X(21)00045-0
PMID: 33862012

62. Molecular characterization of mutations associated with resistance to second

line drugs in Mycobacterium tuberculosis patients from Casablanca, Morocco.

Rev Inst Med Trop Sao Paulo. 2021 Mar 24;63:e19. doi: 10.1590/S1678-9946202163019. eCollection 2021.

Momen G(1)(2), Achraf A(1)(3), Abdelmajid L(1), Fouad C(1), Mohamed B(2), Malika M(1), Khalid B(1), Jamal M(3), Mohammed EM(4), Driss EMM(1), Meriem K(1), Imane C(4).

The emergence and spread of extensively drug-resistant tuberculosis (XDR-TB) is a serious threat to global health. Therefore, its rapid diagnosis is crucial. The present study aimed to characterize mutations conferring resistance to second line drugs (SLDs) within multidrug Mycobacterium tuberculosis (MDR-MTB) isolates and to estimate the occurrence of XDR-TB in Casablanca, Morocco. A panel of 200 MDR-TB isolates was collected at the Pasteur Institute between 2015-2018. Samples were subjected to drug susceptibility testing to Ofloxacin (OFX), Kanamycin (KAN) and Amikacin (AMK). The mutational status of gyrA, gyrB, rrs, tlyA and eis was assessed by sequencing these target genes. Drug susceptibility testing for SLDs showed that among the 200 MDR strains, 20% were resistant to OFX, 2.5% to KAN and 1.5% to AMK. Overall, 14.5% of MDR strains harbored mutations in gyrA, gyrB, rrs and tlyA genes. From the 40 OFXR isolates, 67.5% had mutations in QRDR of gyrA and gyrB genes, the most frequent one being Ala90Val in gyrA gene. Of note, none of the isolates harbored simultaneously mutations in gyrA and gyrB genes. In eight out of the 200 MDR-TB isolates resistant either to KAN or AMK, only 25% had A1401G or Lys89Glu change in rrs and tlyA genes respectively. This study is very informative and provides data on the alarming rate of fluoroquinolone resistance which warrants the need to implement appropriate drug regimens to prevent the emergence and spread of more severe forms of Mycobacterium tuberculosis drug resistance.

DOI: 10.1590/S1678-9946202163019
PMCID: PMC7997671
PMID: 33787739 [Indexed for MEDLINE]

63. Multifaceted role of drugs: a potential weapon to outsmart Mycobacterium tuberculosis resistance by targeting its essential ThyX.

J Biomol Struct Dyn. 2021 Apr 16:1-10. doi: 10.1080/07391102.2021.1913230. Online ahead of print.

Tanweer S(1), Jamal S(1), Mehra S(1), Saqib N(1), Ahmad F(1), Faizan(1), Grover A(2), Grover S(1).

Tuberculosis (TB) is one of the prominent cause of deaths across the world and multidrug-resistant and extensively drug-resistant TB continues to pose challenges for clinicians and public health centers. The risk of death is extremely high in individuals who have compromised immune systems, HIV infection, or diabetes. Research institutes and pharmaceutical companies have been working on repurposing existing drugs as effective therapeutic options against TB. The identification of suitable drugs with multi-target affinity profiles is a widely accepted way to combat the development of resistance. Flavin-dependent thymidylate synthase (FDTS), known as ThyX, is in the class of methyltransferases and is a possible target in the discovery of novel anti-TB drugs. In this study, we aimed to repurpose existing drugs approved by Food and Drug Administration (FDA) that could be used in the treatment of TB. An integrated screening was performed based on computational procedures: high-throughput molecular docking techniques, followed by molecular dynamics simulations of the target enzyme, ThyX. After performing in silico screening using a library of 3,967 FDA-approved drugs, the two highest-scoring drugs, Carglumic acid and Mesalazine, were selected as potential candidates that could be repurposed to treat TB.Communicated by Ramaswamy H. Sarma.

DOI: 10.1080/07391102.2021.1913230
PMID: 33860725

64. Is deployement of diagnostic test alone enough? Comprehensive package of interventions to strengthen TB laboratory network: three years of experience in Burkina Faso.

BMC Infect Dis. 2021 Apr 13;21(1):346. doi: 10.1186/s12879-021-06012-y.

Alagna R(1), Combary A(2), Tagliani E(3), Sawadogo LT(2), Saouadogo T(2), Diandé S(2), Ouedraogo F(2), Cirillo DM(3).

BACKGROUNDS: The laboratory plays a critical role in tuberculosis (TB) control by providing testing for diagnosis, treatment monitoring, and surveillance at each level of the health care system. Weak accessibility to TB diagnosric services still represents a big concern in many limited resources' countries. Here we report the experience of Burkina Faso in implementing a comprehensive intervention packages to strengthen TB laboratory capacity and diagnostic accessibility.
METHODS: The intervention lasted from October 2016 to December 2018 and focused on two main areas: i) development of strategic documents and policies; ii) implementation of TB diagnostic technology. National TB laboratory data were collected between 2016 and 2018 and evaluated according to five programmatic TB laboratory indicators: i) Percentage of notified new and relapse TB cases with

bacteriological confirmation; ii) Percentage of notified new and relapse TB cases tested by Xpert MTB/RIF; iii) Percentage of notified, bacteriologically confirmed TB cases with a drug susceptibility testing (DST) result for rifampin; iv) Percentage of notified MDR-TB cases on the estimated number of MDR-TB cases; v) The ration between the number of smear microscopy and Xpert MTB/RIF tests. We compared these indicators between a 1 year (2016-2017) and 2 years (2016-2018) timeframe.
RESULTS: From 2016 to 2018, the percentage of bacteriologically confirmed cases increased from 67 to 71%. The percentage of new and relapse TB cases notified tested by Xpert MTB/RIF increased from 18% in 2016 to 46% in 2018 and the percentage of bacteriologically confirmed cases with an available DST result for rifampicin increased from 27% in 2016 to 66% in 2018.. The percentage of notified MDR-TB cases on the estimated number of MDR-TB cases in 2018 increased from 43% in 2016 to 78% in 2018. In 2018, the ratio between the number of smear microscopy and Xpert MTB/RIF tests decreased from 53% in 2016 to 21% in 2018.
CONCLUSION: We demonstrated that the implementation of a comprehensive package of laboratory strengthening interventions led to a significant improvement of all indicators. External technical assistance played a key role in speeding up the TB laboratory system improvement process.

DOI: 10.1186/s12879-021-06012-y
PMCID: PMC8042973
PMID: 33849486

65. In silico guided design of non-covalent inhibitors of DprE1: synthesis and biological evaluation.

SAR QSAR Environ Res. 2021 Apr;32(4):333-352. doi: 10.1080/1062936X.2021.1900390.

Verma H(1), Choudhary S(1), Kumar M(1), Silakari O(1).

DprE1 is a potential target of resistant tuberculosis (TB), especially multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB. 2-benzoxazolinone is a closely related bioisostere of some scaffolds such as benzoxazoles, benzimidazole, benzothiazolinone, and benzothiazoles that have been previously explored against DprE1. Thus, a ligand-based quantitative pharmacophore model (AHRR.8) of DprE1 was developed and this pharmacophore model was utilized in activity profiling of some 2-benzoxazolinones from an in-house database using virtual screening. Obtained hits were subject to molecular docking, molecular dynamics (MD), and MM/GBSA calculations, which resulted in benzoyl-substituted derivatives of 2-benzoxazolinone showing strong interactions with the key amino acid residues in the active site of DprE1. Based on in silico

results, the top five hits were duly synthesized and evaluated against the XDR-TB strain. This study is an initial effort to explore 2-benzoxazolinones against XDR-TB, which can be submitted further to lead optimization for refining the results.

DOI: 10.1080/1062936X.2021.1900390
PMID: 33784906

66. Overexpression of mfpA Gene Increases Ciprofloxacin Resistance in Mycobacterium smegmatis.

Int J Microbiol. 2021 Mar 22;2021:6689186. doi: 10.1155/2021/6689186. eCollection 2021.

Falco A(1)(2), Aranaga C(3), Ocampo I(1), Takiff H(1)(4)(5).

Fluoroquinolones (FQs) are antibiotics useful in the treatment of drug-resistant tuberculosis, but FQ-resistant mutants can be selected rapidly. Although mutations in the DNA gyrase are the principal cause of this resistance, pentapeptide proteins have been found to confer low-level FQ resistance in Gram-negative bacteria. MfpA is a pentapeptide repeat protein conserved in mycobacterial chromosomes, where it is adjacent to a group of four highly conserved genes termed a conservon. We wished to characterize the transcriptional regulation of the mfpA gene and relate its expression to ciprofloxacin resistance in M. smegmatis. Reverse transcription PCR showed that mfpA gene is part of an operon containing the conservon genes. Using a transcriptional fusion, we showed that a promoter was located 5' to the mfpEA operon. We determined the promoter activity under different growth conditions and found that the expression of the operon increases slightly in late growth phases in basic pH and in subinhibitory concentrations of ciprofloxacin. Finally, by cloning the mfpA gene in an inducible vector, we showed that induced expression of mfpA increases the ciprofloxacin Minimal Inhibitory Concentration. These results confirm that increased expression of the mfpA gene, which is part of the mfpEA operon, increases ciprofloxacin resistance in M. smegmatis.

DOI: 10.1155/2021/6689186
PMCID: PMC8007378
PMID: 33824663

68. Adverse events using shorter MDR-TB regimens: outcomes from Port Moresby, Papua

New Guinea.

Public Health Action. 2021 Mar 21;11(1):2-4. doi: 10.5588/pha.20.0026.

Mason CY(1), Prieto A(1), Bogati H(1), Sannino L(2), Akai N(1), Marquardt T(3).

Evidence increasingly indicates that standardised, shorter regimens (SR) for multidrug-resistant TB (MDR-TB) is effective in treating this global disease, but there is little published data on associated adverse events. We report outcomes from a cohort treated with the SR in Port Moresby, Papua New Guinea (PNG). Among 26 patients treated with a TB SR from September 2017 to September 2018, 10 (39%) were successful treatments, 12 (46%) were failures, 2 died, and 2 were lost to follow-up. Of those whose treatment failed, most (n = 10) changed their regimen due to adverse events, including seven from ototoxicity, suggesting this SR may not be suited to all patients in PNG and similar settings.

Publisher: Les preuves disponibles montrent de plus en plus que des protocoles standardisés, plus courts (SR) de la TB multirésistante (MDR-TB) traitent efficacement cette maladie mondiale, mais il y a peu de données publiées sur les effets secondaires. Nous rapportons les résultats d'une cohorte traitée par SR à Port Moresby, Papouasie Nouvelle-Guinée (PNG). Parmi 26 patients traités par SR de TB de septembre 2017 à septembre 2018 : 10 (39%) ont été traités avec succès, 12 (46%) ont échoué, 2 sont décédés et 2 ont été perdus de vue. Parmi les échecs, la majorité (n = 10) a changé de protocole en raison d'effets secondaires, notamment sept patients pour ototoxicité, suggérant que ce protocole standardisé n'était pas forcément adapté à tous les patients en PNG et dans des contextes similaires.

DOI: 10.5588/pha.20.0026
PMCID: PMC7987249
PMID: 33777714

69. Identification of Novel Tricyclic Benzo[1,3]oxazinyloxazolidinones as Potent Antibacterial Agents with Excellent Pharmacokinetic Profiles against Drug-Resistant Pathogens.

J Med Chem. 2021 Mar 25;64(6):3234-3248. doi: 10.1021/acs.jmedchem.0c02153. Epub 2021 Mar 11.

Wu Y(1)(2), Wang B(3), Lu H(1)(2), Zhao H(1)(2), Yang B(1), Li L(1), Lu Y(3),

Zhang D(1)(2), Sun N(4)(5), Huang H(1)(2).

A series of conformationally constrained novel benzo[1,3]oxazinyloxazolidinones were designed, synthesized, and evaluated on their activities against Mycobacterium tuberculosis, Gram-positive bacteria, and Gram-negative bacteria. The studies identified a new compound 20aa that displayed good to excellent antibacterial and antitubercular profiles against drug-resistant TB strains (MIC = 0.48-0.82 μg/mL), MRSA (MIC = 0.25-0.5 μg/mL), MRSE (MIC = 1 μg/mL), VISA (MIC = 0.25 μg/mL), and VRE (MIC = 0.25 μg/mL) and some linezolid-resistant strains (MIC 1-2 μg/mL). Compound 20aa was demonstrated as a promising candidate through ADME/T evaluation including microsomal stability, cytotoxicity, and inhibition of hERG and monoamine oxidase. Notably, 20aa showed excellent mouse PK profile with high plasma exposure (AUC0-∞ = 78 669 h·ng/mL), high peak plasma concentration (Cmax = 10 253 ng/mL), appropriate half-life of 3.76 h, and superior oral bioavailability (128%). The present study not only successfully provides a novel benzo[1,3]oxazinyloxazolidinone scaffold with superior druggability but also lays a good foundation for new antibacterial drug development.

DOI: 10.1021/acs.jmedchem.0c02153
PMID: 33705128

70. Building resilience needs to be central to treating drug-resistant tuberculosis.

Lancet Glob Health. 2021 Apr;9(4):e381-e382. doi: 10.1016/S2214-109X(21)00056-5.

Cox H(1), Loveday M(2).

Comment on
Lancet Glob Health. 2021 Apr;9(4):e479-e488.

DOI: 10.1016/S2214-109X(21)00056-5
PMID: 33740401 [Indexed for MEDLINE]

71. Inhibitors of F(1)F(0)ATP synthase enzymes for the treatment of tuberculosis and cancer.

Future Med Chem. 2021 Apr 13. doi: 10.4155/fmc-2021-0010. Online ahead of print.

Denny WA(1)(2).

The spectacular success of the mycobacterial F1F0-ATP synthase inhibitor

bedaquiline for the treatment of drug-resistant tuberculosis has generated wide interest in the development of other inhibitors of this enzyme. Work in this realm has included close analogues of bedaquiline with better safety profiles and 'bedaquiline-like' compounds, some of which show potent antibacterial activity in vitro although none have yet progressed to clinical trials. The search has lately extended to a range of new scaffolds as potential inhibitors, including squaramides, diaminoquinazolines, chloroquinolines, dihydropyrazolo[1,5-a]pyrazin-4-ones, thiazolidinediones, diaminopyrimidines and tetrahydroquinolines. Because of the ubiquitous expression of ATP synthase enzymes, there has also been interest in inhibitors of other bacterial ATP synthases, as well as inhibitors of human mitochondrial ATP synthase for cancer therapy. The latter encompass both complex natural products and simpler small molecules. The review seeks to demonstrate the breadth of the structural types of molecules able to effectively inhibit the function of variants of this intriguing enzyme.

DOI: 10.4155/fmc-2021-0010
PMID: 33845594

72. Outcomes of Children Born to Pregnant Women With Drug-resistant Tuberculosis Treated With Novel Drugs in Khayelitsha, South Africa: A Report of Five Patients.

Pediatr Infect Dis J. 2021 May 1;40(5):e191-e192. doi: 10.1097/INF.0000000000003069.

Acquah R(1), Mohr-Holland E(1), Daniels J(1), Furin J(2), Loveday M(3), Mudaly V(4), Reuter A(1).

This brief report presents a series of 5 pregnant women treated for rifampicin-resistant tuberculosis with the novel drugs bedaquiline, delamanid, and linezolid as part of an optimized backbone regimen and reviews the outcomes of the children born to them. Although the case series is small, all children had excellent birth outcomes suggesting pregnant women should not be denied access to novel therapies for RR-TB.

DOI: 10.1097/INF.0000000000003069
PMCID: PMC8043512
PMID: 33847295

73. Ringing the alarm bell: Time to scale up drug-resistant tuberculosis preventive treatment.

EClinicalMedicine. 2021 Apr 6;34:100821. doi: 10.1016/j.eclinm.2021.100821. eCollection 2021 Apr.

Malik AA(1)(2), Becerra MC(3), Hussain H(4).

DOI: 10.1016/j.eclinm.2021.100821
PMCID: PMC8027541
PMID: 33855286