Literature

1. Multidrug-Resistant Tuberculosis in U.S.-Bound Immigrants and Refugees.

Ann Am Thorac Soc. 2022 Jun;19(6):943-951. doi: 10.1513/AnnalsATS.202105-580OC.

Liu Y(1), Posey DL(1), Yang Q(2), Weinberg MS(1), Maloney SA(3), Lambert LA(4), Ortega LS(1), Marano N(1), Cetron MS(1), Phares CR(1).

Rationale: Approximately two-thirds of new cases of tuberculosis (TB) in the United States are among non-U.S.-born persons. Culture-based overseas TB screening in U.S.-bound immigrants and refugees has substantially reduced the importation of TB into the United States, but it is unclear to what extent this program prevents the importation of multidrug-resistant TB (MDR-TB). Objectives: To study the epidemiology of MDR-TB in U.S.-bound immigrants and refugees and to evaluate the effect of culture-based overseas TB screening in U.S.-bound immigrants and refugees on reducing the importation of MDR-TB into the United States. Methods: We analyzed data of immigrants and refugees who completed overseas treatment for culture-positive TB during 2015-2019. We also compared mean annual number of MDR-TB cases in non-U.S.-born persons within 1 year of arrival in the United States between 1996-2006 (when overseas screening followed a smear-based algorithm) and 2014-2019 (after full implementation of a culture-based algorithm). Results: Of 3,300 culture-positive TB cases identified by culture-based overseas TB screening in immigrants and refugees during 2015-2019, 122 (3.7%; 95% confidence interval [CI], 3.1-4.1) had MDR-TB, 20 (0.6%; 95% CI, 0.3-0.9) had rifampicin-resistant TB, 382 (11.6%; 95% CI, 10.5-12.7) had isoniazid-resistant TB, and 2,776 (84.1%; 95% CI, 82.9-85.4) had rifampicin- and isoniazid-susceptible TB. None were diagnosed with extensively drug-resistant TB. All 3,300 persons with culture-positive TB completed treatment overseas; of 70 and 11 persons who were treated overseas for MDR-TB and rifampicin-resistant TB, respectively, none were diagnosed with TB disease at postarrival evaluation in the United States. Culture-based overseas TB screening in U.S.-bound immigrants and refugees prevented 24.4 MDR-TB cases per year from arriving in the United States, 18.2 cases more than smear-based overseas TB screening. The mean annual number of MDR-TB cases among non-U.S.-born persons within 1 year of arrival in the United States decreased from 34.6 cases in 1996-2006 to 19.5 cases in 2014-2019 (difference of 15.1; $P < 0.001$). Conclusions: Culture-based overseas TB screening in U.S.-bound immigrants and refugees substantially reduced the importation of MDR-TB into the United States.

DOI: 10.1513/AnnalsATS.202105-580OC
PMCID: PMC9169124

PMID: 34941475 [Indexed for MEDLINE]

2. Bedaquiline-containing regimens and multidrug-resistant tuberculosis: a systematic review and meta-analysis.

J Bras Pneumol. 2022 May 30;48(2):e20210384. doi: 10.36416/1806-3756/e20210384. eCollection 2022.

Hatami H(1), Sotgiu G(2), Bostanghadiri N(3), Abadi SSD(4), Mesgarpour B(5), Goudarzi H(4), Migliori GB(6), Nasiri MJ(4).

OBJECTIVE: Multidrug-resistant tuberculosis (MDR-TB) is a life-threatening infectious disease. Treatment requires multiple antimicrobial agents used for extended periods of time. The present study sought to evaluate the treatment success rate of bedaquiline-based regimens in MDR-TB patients.
METHODS: This was a systematic review and meta-analysis of studies published up to March 15, 2021. The pooled treatment success rates and 95% CIs were assessed with the fixed-effect model or the random-effects model. Values of $p < 0.05$ were considered significant for publication bias.
RESULTS: A total of 2,679 articles were retrieved by database searching. Of those, 29 met the inclusion criteria. Of those, 25 were observational studies (including a total of 3,536 patients) and 4 were experimental studies (including a total of 440 patients). The pooled treatment success rate was 74.7% (95% CI, 69.8-79.0) in the observational studies and 86.1% (95% CI, 76.8-92.1; $p = 0.00$; $I2 = 75\%$) in the experimental studies. There was no evidence of publication bias ($p > 0.05$).
CONCLUSIONS: In patients with MDR-TB receiving bedaquiline, culture conversion and treatment success rates are high even in cases of extensive resistance.

OBJETIVO: A tuberculose multirresistente (MDR-TB, do inglês multidrug-resistant tuberculosis) é uma doença infecciosa potencialmente fatal. O tratamento exige múltiplos agentes antimicrobianos usados durante longos períodos. O presente estudo buscou avaliar a taxa de sucesso de esquemas terapêuticos com bedaquilina em pacientes com MDR-TB.
MÉTODOS: Trata-se de uma revisão sistemática e meta-análise de estudos publicados até 15 de março de 2021. As taxas combinadas de sucesso do tratamento e os IC95% foram avaliados por meio do modelo de efeito fixo ou do modelo de efeitos aleatórios. Valores de $p < 0,05$ foram considerados significativos para viés de publicação.
RESULTADOS: Por meio de buscas eletrônicas em bancos de dados, foram recuperados 2.679 artigos. Destes, 29 preencheram os critérios de inclusão. Destes, 25 eram estudos observacionais (com um total de 3.536 pacientes) e 4 eram estudos experimentais (com um total de 440 pacientes). A taxa combinada de sucesso do

tratamento foi de 74,7% (IC95%: 69,8-79,0) nos estudos observacionais e de 86,1% (IC95%: 76,8-92,1; p = 0,00; I2 = 75%) nos estudos experimentais. Não foram encontradas evidências de viés de publicação (p > 0,05).
CONCLUSÕES: Em pacientes com MDR-TB tratados com bedaquilina, as taxas de conversão da cultura e sucesso do tratamento são altas mesmo em casos de resistência extensa.

DOI: 10.36416/1806-3756/e20210384
PMCID: PMC8836629
PMID: 35649043 [Indexed for MEDLINE]

3. Drug-resistant tuberculosis: Promising progress with a note of caution.

Indian J Med Res. 2022 Jun 1. doi: 10.4103/ijmr.ijmr_677_22. Online ahead of print.

Esmail H(1), Narendran G(2), Nunn A(3).

DOI: 10.4103/ijmr.ijmr_677_22
PMID: 35647946

Conflict of interest statement: None

4. Clinical Features and Outcome of Multidrug-Resistant Osteoarticular Tuberculosis: A 12-Year Case Series from France.

Microorganisms. 2022 Jun 14;10(6):1215. doi: 10.3390/microorganisms10061215.

Bonnet I(1)(2)(3), Haddad E(4), Guglielmetti L(1)(2)(3), Bémer P(5), Bernard L(6), Bourgoin A(7), Brault R(8), Catho G(9), Caumes E(4), Escaut L(10), Fourniols E(11), Fréchet-Jachym M(12), Gaudart A(13), Guillot H(14), Lafon-Desmurs B(15), Lanoix JP(16), Lanotte P(17), Lemaignen A(6), Lemaire B(12), Lemaitre N(18), Michau C(19), Morand P(20), Mougari F(21), Marigot-Outtandy D(12), Patrat-Delon S(22), Perpoint T(9), Piau C(23), Pourcher V(4), Zarrouk V(24), Zeller V(25), Veziris N(1)(2)(3)(26), Jauréguiberry S(4)(10)(27), Aubry A(1)(2)(3)(27); CRIOAC Pitié-Salpêtrière and the TB Consilium of the National Reference Center for Mycobacteria.

The optimal treatment for osteoarticular infection due to multidrug-resistant tuberculosis strains (MDR-OATB) remains unclear. This study aims to evaluate the diagnosis, management and outcome of MDR-OATB in France. We present a case series of MDR-OATB patients reviewed at the French National Reference Center for Mycobacteria between 2007 and 2018. Medical history and clinical, microbiological, treatment and outcome data were collected. Twenty-three

MDR-OATB cases were reported, representing 3% of all concurrent MDR-TB cases in France. Overall, 17 were male, and the median age was 32 years. Six patients were previously treated for TB, including four with first-line drugs. The most frequently affected site was the spine (n = 16). Bone and joint surgery were required in 12 patients. Twenty-one patients (91%) successfully completed the treatment with a regimen containing a mean of four drugs (range, 2-6) for a mean duration of 20 months (range, 13-27). Overall, high rates of treatment success were achieved following WHO MDR-TB treatment guidelines and individualized patient management recommendations by the French National TB Consilium. However, the optimal combination of drugs, duration of treatment and role of surgery in the management of MDR-OATB remains to be determined.

DOI: 10.3390/microorganisms10061215
PMCID: PMC9229793
PMID: 35744731

Conflict of interest statement: The authors declare no conflict of interest. The funder had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

5. Risk factors for multidrug-resistant tuberculosis: A worldwide systematic review and meta-analysis.

PLoS One. 2022 Jun 16;17(6):e0270003. doi: 10.1371/journal.pone.0270003. eCollection 2022.

Xi Y(1), Zhang W(2), Qiao RJ(1), Tang J(1).

BACKGROUND: Since multidrug-resistant tuberculosis (MDR-TB) is a significant public health problem worldwide, identifying associated risk factors is critical for developing appropriate control strategies.
METHODS: A systematic review and meta-analysis was conducted for identifying factors independently predicting MDR-TB. The random-effects model was used to determine pooled odds ratios (ORs) and respective 95% confidence intervals (CIs) for the related factors.
RESULTS: Of the 2301 retrieved reports, 28 studies were analyzed, assessing 3152 MDR-TB and 52715 DS-TB cases. Totally 22 related factors were analyzed. The pooled ORs were 1.478 (95%CI 1.077-2.028) for positive sputum AFB smear, 1.716 (95%CI 1.149-2.564) for lung cavity, 6.078 (95%CI 2.903-12.725) for previous TB disease and 5.427 (95%CI 3.469-8.490) for a history of anti-TB therapy. All Z test p values were below 0.05, indicating these parameters were significantly associated with MDR-TB.

CONCLUSIONS: Positive sputum AFB smear, lung cavity, previously diagnosed TB and a history of anti-TB therapy are significant risk factors for MDR-TB, which are independent of the clinical setting worldwide. Increased attention should be paid to cases with such parameters to achieve more effective TB control and avoid MDR-TB through the development of a global policy.

DOI: 10.1371/journal.pone.0270003
PMCID: PMC9202901
PMID: 35709161 [Indexed for MEDLINE]

6. 25 years of surveillance of drug-resistant tuberculosis: achievements, challenges, and way forward.

Lancet Infect Dis. 2022 Jul;22(7):e191-e196. doi: 10.1016/S1473-3099(21)00808-2. Epub 2022 Mar 3.

Dean AS(1), Tosas Auguet O(2), Glaziou P(2), Zignol M(2), Ismail N(2), Kasaeva T(2), Floyd K(2).

Comment in
Lancet Infect Dis. 2022 Jun;22(6):760.

Tuberculosis is second only to COVID-19 as a cause of death from a single infectious agent. In 2020, almost 10 million people were estimated to have developed tuberculosis and it caused 1·5 million deaths. Around a quarter of deaths caused by antimicrobial resistance are due to rifampicin-resistant tuberculosis. Antimicrobial resistance surveillance systems for many bacterial pathogens are still in the early stages of implementation in many countries, and do not yet allow for the estimation of disease burden at the national level. In this Personal View, we present the achievements, challenges, and way forward for the oldest and largest global antimicrobial resistance surveillance system. Hosted by WHO since 1994, the Global Project on Anti-Tuberculosis Drug Resistance Surveillance has served as a platform for the evaluation of the trends in anti-tuberculosis drug resistance for over 25 years at country, regional, and global levels. With an estimated 465 000 incident cases of multidrug-resistant and rifampicin-resistant tuberculosis in 2019, drug-resistant tuberculosis remains a public health crisis. The COVID-19 pandemic has reversed years of progress in providing essential tuberculosis services and reducing disease burden. The number of people diagnosed with drug-resistant tuberculosis has dropped by 22% since before the pandemic, and the number of patients provided with treatment for drug-resistant tuberculosis has dropped by 15%. Now more than ever, closing gaps in the detection of drug-resistant tuberculosis requires investment in research and development of new diagnostic tools and their rollout, expansion of sample transport systems,

and the implementation of data connectivity solutions.

DOI: 10.1016/S1473-3099(21)00808-2
PMCID: PMC8893725
PMID: 35248168

7. Improved Conventional and New Approaches in the Diagnosis of Tuberculosis.

Front Microbiol. 2022 May 31;13:924410. doi: 10.3389/fmicb.2022.924410. eCollection 2022.

Dong B(1), He Z(1), Li Y(2), Xu X(1), Wang C(1), Zeng J(1).

Tuberculosis (TB) is a life-threatening infectious disease caused by Mycobacterium tuberculosis (M. tuberculosis). Timely diagnosis and effective treatment are essential in the control of TB. Conventional smear microscopy still has low sensitivity and is unable to reveal the drug resistance of this bacterium. The traditional culture-based diagnosis is time-consuming, since usually the results are available after 3-4 weeks. Molecular biology methods fail to differentiate live from dead M. tuberculosis, while diagnostic immunology methods fail to distinguish active from latent TB. In view of these limitations of the existing detection techniques, in addition to the continuous emergence of multidrug-resistant and extensively drug-resistant TB, in recent years there has been an increase in the demand for simple, rapid, accurate and economical point-of-care approaches. This review describes the development, evaluation, and implementation of conventional diagnostic methods for TB and the rapid new approaches for the detection of M. tuberculosis.

DOI: 10.3389/fmicb.2022.924410
PMCID: PMC9195135
PMID: 35711765

8. Disadvantage and the Experience of Treatment for Multidrug-Resistant Tuberculosis (MDR-TB).

SSM Qual Res Health. 2022 Dec;2:100042. doi: 10.1016/j.ssmqr.2022.100042. Epub 2022 Jan 28.

Taylor HA(1), Dowdy DW(2), Searle AR(3), Stennett AL(3), Dukhanin V(1), Zwerling AA(4), Merritt MW(5).

DOI: 10.1016/j.ssmqr.2022.100042

PMCID: PMC8896740
PMID: 35252955

Conflict of interest statement: Declarations of Conflicts of Interest: None

9. The way forward for drug-resistant tuberculosis in the Philippines.

Lancet Infect Dis. 2022 Jun;22(6):760. doi: 10.1016/S1473-3099(22)00285-7.

Bernardo MNG(1), Alberto IRI(1), Alberto NRI(1), Eala MAB(1), Roa CC Jr(2).

Comment on
Lancet Infect Dis. 2022 Mar 3;:null.

DOI: 10.1016/S1473-3099(22)00285-7
PMCID: PMC9132560
PMID: 35643095 [Indexed for MEDLINE]

Conflict of interest statement: We declare no competing interests.

10. **Prevalence and Drug Resistance Pattern of Mycobacterium tuberculosis Isolated from Tuberculosis Patients in Basra, Iraq.**

Pol J Microbiol. 2022 May 31;71(2):205-215. doi: 10.33073/pjm-2022-018.

Mohammed KAS(1), Khudhair GS(1), Al-Rabeai DB(2).

Drug-resistant Mycobacterium tuberculosis (DR-MTB) is a major health threat to human beings. This study aimed to evaluate the prevalence and drug resistance profile of MTB. Data were collected from 2,296 newly diagnosed, and 246 retreated tuberculosis (TB) patients who attended the Advisory Clinic for Chest Diseases and Respiratory in Basra province from January 2016 to December 2020. Both new diagnostic and retreated TB cases showed that DR-MTB cases were significantly higher at age 15-34 years, pulmonary TB, and urban residents but with no significant difference regarding gender. The drugs resistance was significantly higher among the retreated cases compared with the new diagnostic patients (20.3% vs. 2.4%, $p < 0.0001$), with the percentage of the resistance to first-line drugs in primary and secondary cases including isoniazid (1% and 17.1%), rifampicin (0.78% and 15.8%), ethambutol (0.56% and 8.5%), streptomycin (1.3% and 9.75%). Notice that the most common drug resistance was against streptomycin with 1.3% in new patients and against isoniazid (17.1%) in retreated patients. The rate of total drug-resistant TB, multi-drug resistant TB, mono-drug resistant TB, and rifampicin-resistant TB among new tuberculosis cases increased in this period from 2.2 to 6.7%, 0.17 to 1.6%, 0.85 to 4%, and

0.17 to 4%, with a percentage change of 204.54, 841.17, 370.58, 22.5%, respectively. The rates of poly drug-resistant TB and ethambutol-resistant-TB dropped in this period by 15.96%, and 0.7%, with a decrease from 1.19 to 1% and from 1 to 0.3%, respectively. Similarly, the increase of drug-resistant TB among secondary cases has also occurred. In conclusion, the temporal trend showed an increase in the rate of drug resistance of M. tuberculosis since 2016, with a predominant multi-drug-resistant TB and isoniazid-resistant TB.

DOI: 10.33073/pjm-2022-018
PMID: 35675816 [Indexed for MEDLINE]

11. **Linezolid Pharmacokinetics/Pharmacodynamics-Based Optimal Dosing for Multidrug-Resistant Tuberculosis.**

Int J Antimicrob Agents. 2022 Jun;59(6):106589. doi: 10.1016/j.ijantimicag.2022.106589. Epub 2022 Apr 9.

Zhou W(1), Nie W(1), Wang Q(1), Shi W(1), Yang Y(1), Li Q(1), Zhu H(2), Liu Z(2), Ding Y(2), Lu Y(3), Chu N(4).

OBJECTIVES: Linezolid can significantly impact drug-resistant tuberculosis (DR-TB) patient outcomes. However, the long-term use of this drug for TB treatment has been limited by adverse reactions and uncertainty regarding optimal dosage regimens for balancing drug efficacy and safety across different populations. This study attempted to find the optimal dosing regimen of linezolid in different populations.
METHODS: A total of 355 blood samples were collected from 126 DR-TB patients. Population pharmacokinetic analysis (using a one-compartment model) and dose simulations were conducted using NONMEM and R software. The ratio between the area under the free drug plasma concentration-time curve to the MIC (fAUC/MIC) of > 119 and trough concentration (Cmin) ≤ 2 mg/L served as efficacy and safety targets, respectively, toward the formulation of optimal dosage regimens based on a ≥ 90% cumulative fraction of response.
RESULTS: Body weight and blood urea nitrogen levels were the most significant covariates of apparent volume, while creatinine clearance and haemoglobin level significantly influenced apparent clearance. The probability of target attainment for different dosage regimens was evaluated via Monte Carlo simulation. For subjects with MICs of 0.125, 0.25 and 0.5 mg/L, specific total daily doses of ≥ 300 mg, ≥ 450 mg and ≥ 900 mg were required to reach the target, respectively. Subjects with body weight ≤ 70 kg and MIC ≥ 1 mg/L received a total 1200 mg daily dose to reach the probability of target attainment target. Notably, single dosing was safer than multiple dosing at the

same daily dose. The optimal dosage regimens for subjects with body weight < 50 kg and ≥ 50 kg were 450 mg/d and 600 mg/d (once daily), respectively.
CONCLUSION: Optimal dosage regimens for patients weighing < 50 kg and ≥ 50 kg were 450 mg/d and 600 mg/d, respectively. A single dose was safer than multiple doses.

DOI: 10.1016/j.ijantimicag.2022.106589
PMID: 35405268 [Indexed for MEDLINE]

12. **Continuous surveillance of drug-resistant TB burden in Rwanda: a retrospective cross-sectional study.**

Int Health. 2022 Jun 2:ihac039. doi: 10.1093/inthealth/ihac039. Online ahead of print.

Habimana-Mucyo Y(1), Dushime A(1), Migambi P(1), Habiyambere I(1), Semuto Ngabonziza JC(2)(3), Decroo T(4).

BACKGROUND: Since the roll-out of the Xpert MTB/RIF assay, continuous surveillance can provide an estimate of rifampicin-resistant TB (RR-TB) prevalence, provided high drug susceptibility testing (DST) coverage is achieved. We use national data from Rwanda to describe rifampicin DST coverage, estimate the prevalence of RR-TB and assess its predictors.
METHODS: Routinely collected DST data were entered into an electronic TB case-based surveillance system. DST coverage was calculated among all bacteriologically confirmed pulmonary TB patients notified from 1 July 2019 to 30 June 2020 in Rwanda. The prevalence of RR-TB was estimated among those with DST results. Univariable and multivariable analysis was performed to explore predictors for RR TB.
RESULTS: Among 4066 patients with bacteriologically confirmed pulmonary TB, rifampicin DST coverage was 95.6% (4066/4251). RR-TB was diagnosed in 73 patients. The prevalence of RR-TB was 1.4% (53/3659; 95% CI 1.09 to 1.89%) and 4.9% (20/406; 95% CI 3.03 to 7.51%) in new and previously treated TB cases, respectively. Predictors of RR-TB were: (1) living in Kigali City (adjusted OR [aOR] 1.65, 95% CI 1.03 to 2.65); (2) previous TB treatment (aOR 3.64, 95% CI 2.14 to 6.19); and (3) close contact with a known RR-TB patient (aOR 11.37, 95% CI 4.19 to 30.82).
CONCLUSIONS: High rifampicin DST coverage for routine reporting allowed Rwanda to estimate the RR-TB prevalence among new and previously treated patients.

DOI: 10.1093/inthealth/ihac039
PMID: 35653710

13. **Whole-Genome Sequencing for Resistance Level Prediction in Multidrug-Resistant Tuberculosis.**

Microbiol Spectr. 2022 Jun 6:e0271421. doi: 10.1128/spectrum.02714-21. Online ahead of print.

Li J(#)(1), Yang T(#)(2), Hong C(1), Yang Z(1), Wu L(1), Gao Q(2), Yang H(1), Tan W(1).

Defining the precise relationship between resistance mutations and quantitative phenotypic drug susceptibility testing will increase the value of whole-genome sequencing (WGS) for predicting tuberculosis drug resistance. However, a large number of WGS data sets currently lack corresponding quantitative phenotypic data-the MICs. Using MYCOTBI plates, we determined the MICs to nine antituberculosis drugs for 154 clinical multidrug-resistant tuberculosis isolates from the Shenzhen Center for Chronic Disease Control in Shenzhen, China. Comparing MICs with predicted drug-resistance profiles inferred by WGS showed that WGS could predict the levels of resistance to isoniazid, rifampicin, streptomycin, fluoroquinolones, and aminoglycosides. We also found some mutations that may not be associated with drug resistance, such as EmbB D328G, mutations in the gid gene, and C-12T in the eis promoter. However, some strains carrying the same mutations showed different levels of resistance to the corresponding drugs. The MICs of different strains with the RpsL K88R, fabG1 C-15T mutations and some with mutations in embB and rpoB, had MICs to the corresponding drugs that varied by 8-fold or more. This variation is unexplained but could be influenced by the bacterial genetic background. Additionally, we found that 32.3% of rifampicin-resistant isolates were rifabutin-susceptible, particularly those with rpoB mutations H445D, H445L, H445S, D435V, D435F, L452P, S441Q, and S441V. Studying the influence of bacterial genetic background on the MIC and the relationship between rifampicin-resistant mutations and rifabutin resistance levels should improve the ability of WGS to guide the selection of medical treatment regimens. IMPORTANCE Whole-genome sequencing (WGS) has excellent potential in drug-resistance prediction. The MICs are essential indications of adding a particular antituberculosis drug dosage or changing the entire treatment regimen. However, the relationship between many known drug-resistant mutations and MICs is unclear, especially for rarer ones. The results showed that WGS could predict resistance levels to isoniazid, rifampicin, streptomycin, fluoroquinolones, and aminoglycosides. However, some mutations may not be associated with drug resistance, and some others may confer

various MICs to strains carrying them. Also, 32.3% of rifampicin (RIF)-resistant strains were classified as sensitive to rifabutin (RFB), and some mutations in the rpoB gene may be associated with this phenotype. Our data on the MIC distribution of strains with some rarer mutations add to the accumulated data on the resistance level associated with such mutations to help guide further research and draw meaningful conclusions.

DOI: 10.1128/spectrum.02714-21
PMID: 35658579

14. **Multidrug-Resistant Tuberculosis Treatment Outcome and Associated Factors at the University of Gondar Comprehensive Specialized Hospital: A Ten-Year Retrospective Study.**

Infect Drug Resist. 2022 Jun 3;15:2891-2899. doi: 10.2147/IDR.S365394. eCollection 2022.

Belachew T(1), Yaheya S(2), Tilahun N(2), Gebrie E(2), Seid R(2), Nega T(3), Biset S(1).

BACKGROUND: Multidrug-resistant tuberculosis (MDR-TB) remains a public health crisis and a health security threat worldwide. Poor public health infrastructure, inefficient infection control and mismanagement of TB treatment are among the reasons for the continuous emergence and spread of drug-resistant TB (DR-TB). The final treatment outcome is the most direct measurement of TB control programs. Therefore, this study sought to determine the proportions and predictors of TB treatment outcomes among MDR/RR-TB treated patients.
METHODS: A 10-year, 2011 to 2021, hospital-based retrospective cohort study was conducted at the University of Gondar Comprehensive Specialized Hospital. The records of 408 MDR-TB patients, 389 with treatment outcome and 19 on treatment, were collected using a structured checklist.
RESULTS: A total of 389 patients with a recorded MDR/RR-TB treatment outcome were included. The treatment success rate was 77.12%, with 58.35% cured and 18.76% treatment completed. The proportion of death rate, treatment default loss to follow-up, treatment failure, and unknown treatment outcome was 9.25%, 6.94%, 3.1%, and 3.6%, respectively. Regarding the patient category, the most successful treatment outcome (83.5%) came from patients diagnosed with relapse cases, followed by new cases (81.8%). An unsuccessful treatment outcome was significantly associated with patients aged >44 years (AOR, 3.3, 95% CI = 1.55-6.99).
CONCLUSION AND RECOMMENDATIONS: This study indicated that nearly 23% of MDR/RR-TB patients had unsuccessful treatment outcomes and being older was significantly correlated with these outcomes. For better outcomes, it is recommended to strengthen combined treatment adherence interventions and

evaluate treatment regimens and administration options. A prospective cohort study may be required to investigate the full range of potential causes of unfavorable outcomes.

DOI: 10.2147/IDR.S365394
PMCID: PMC9172731
PMID: 35686191

15. **In vitro activity of fidaxomicin against nontuberculosis mycobacteria.**

J Med Microbiol. 2022 Jun;71(6). doi: 10.1099/jmm.0.001549.

Sun Q(1), Liao X(1), Wang C(1), Jiang G(1), Yang J(2), Zhao J(2), Huang H(1), Wang G(1), Li H(3)(4).

Introduction. Nontuberculous mycobacteria (NTM) infections are increasing worldwide and are relatively resistant to many of the first- and second-line drugs to treat tuberculosis. Macrolide antibiotics, such as clarithromycin and azithromycin, are the key drugs for treating NTM infections. Fidaxomicin is a macrolide antibiotic that is widely used in treating Clostridium difficle (C.difficile) infections, and has high in vitro activity against Mycobacterium tuberculosis especially multidrug-resistant tuberculosis (MDR-TB) and has no cross-resistance with rifampicin.Hypothesis. Fidaxomicin may have in vitro activity against NTM strains.Aim. To find that whether the macrolide antibiotic fidaxomicin has in vitro activity against NTM strains.Methodology. Fidaxomicin used in this study was firstly tested on C. difficile reference strains and has shown to be effective and workable. And then 28 rapidly growing mycobacteria (RGM), 12 slowly growing mycobacteria (SGM) reference strains and 103 NTM clinical isolates were tested by the microplate-based AlamarBlue assay (MABA) method to determine the MICs. Fidaxomicin, rifampicin and clarithromycin were tested against M. abcessus complex subspecies 14 M. abscessus and 5 M. massiliense strains for inducible resistance determination.Results. In total, 21 out of 28 RGM and 9 of 12 SGM reference strains have the MICs of fidaxomicin at or below 1 µg ml-1. Fidaxomicin also showed low MIC values for some clinical isolates including M. abscessus complex, M. avium complex, M. fortuitum, M. kansasii and M. parascrofulaceum. Fidaxomicin also has no inducible macrolide resistance in M. abscessus complex in comparison with clarithromycin.Conclusion. Fidaxomicin has high in vitro activity against most of the NTM reference strains and some prevalent NTM clinical isolates. This promising finding warrants further investigation on the actions of fidaxomicn in vivo and as a potential antibiotic for NTM treatment.

DOI: 10.1099/jmm.0.001549
PMID: 35708979 [Indexed for MEDLINE]

16. **Treatment Outcomes Among Pregnant Patients With Multidrug-Resistant Tuberculosis: A Systematic Review and Meta-analysis.**

JAMA Netw Open. 2022 Jun 1;5(6):e2216527. doi: 10.1001/jamanetworkopen.2022.16527.

Alene KA(1)(2), Murray MB(3), van de Water BJ(4), Becerra MC(3), Atalell KA(5), Nicol MP(6)(7), Clements ACA(1)(2).

IMPORTANCE: The management of multidrug-resistant tuberculosis (MDR-TB) during pregnancy is challenging, yet no systematic synthesis of evidence has accurately measured treatment outcomes.
OBJECTIVE: To systematically synthesize treatment outcomes and adverse events among pregnant patients with MDR-TB.
DATA SOURCES: PubMed, Scopus, Web of Science, and ProQuest were searched from the inception of each database through August 31, 2021.
STUDY SELECTION: Studies containing cohorts of pregnant patients with a defined treatment outcome were eligible.
DATA EXTRACTION AND SYNTHESIS: Independent reviewers screened studies and assessed the risk of bias. The study followed the Preferring Reporting Items for Systematic Review and Meta-analyses reporting guideline. Meta-analysis was performed using random-effects models. The sources of heterogeneity were explored through metaregression.
MAIN OUTCOMES AND MEASURES: The primary outcome was the proportion of patients with each treatment outcome (including treatment success, death, loss to follow-up, and treatment failure), and the secondary outcomes included the proportion of patients experiencing adverse events during pregnancy.
RESULTS: In this systematic review and meta-analysis, 10 studies containing 275 pregnant patients with available data on treatment outcomes were included. The pooled estimate was 72.5% (95% CI, 63.3%-81.0%) for treatment success, 6.8% (95% CI, 2.6%-12.4%) for death, 18.4% (95% CI, 13.1%-24.2%) for loss to follow-up, and 0.6% (95% CI, 0.0%-2.9%) for treatment failure. Treatment success was significantly higher in studies in which the proportion of patients taking linezolid was greater than the median (20.1%) compared with studies in which this proportion was lower than the median (odds ratio, 1.22; 95% CI, 1.05-1.42). More than half of the pregnant patients (54.7%; 95% CI, 43.5%-65.4%) experienced at least 1 type of adverse event, most commonly liver function impairment (30.4%; 95% CI, 17.7%-45.7%), kidney function impairment (14.9%; 95% CI, 6.2%-28.3%), hypokalemia (11.9%; 95% CI, 3.9%-25.6%), hearing loss (11.8%; 95% CI, 5.5%-21.3%), gastrointestinal disorders (11.8%; 95% CI, 5.2%-21.8%),

psychiatric disorders (9.1%; 95% CI, 2.5%-21.6%), or anemia (8.9%; 95% CI, 3.6%-17.4%). The pooled proportion of favorable pregnancy outcomes was 73.2% (95% CI, 49.4%-92.1%). The most common types of adverse pregnancy outcomes were preterm birth (9.5%; 95% CI, 0.0%-29.0%), pregnancy loss (6.0%; 95% CI, 1.3%-12.9%), low birth weight (3.9%; 95% CI, 0.0%-18.7%), and stillbirth (1.9%; 95% CI, 0.1%-5.1%). Most of the studies had low-quality (3 studies) or medium-quality (4 studies) scores.
CONCLUSIONS AND RELEVANCE: In this systematic review and meta-analysis, high treatment success and favorable pregnancy outcomes were reported among pregnant patients with MDR-TB. Further research is needed to design shorter, more effective, and safer treatment regimens for pregnant patients with MDR-TB.

DOI: 10.1001/jamanetworkopen.2022.16527
PMCID: PMC9187956
PMID: 35687333 [Indexed for MEDLINE]

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

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

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

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

was observed in the year 2020 and we alert the Nigerian authorities that COVID-19 control efforts going hand-in-hand with intensified TB case finding and surveillance efforts and initiating proper TB treatment for persons with active TB are urgently needed.

DOI: 10.1016/j.jctube.2022.100319
PMCID: PMC9110314
PMID: 35599722

Conflict of interest statement: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

18. **Insight Into Novel Anti-tuberculosis Vaccines by Using Immunoinformatics Approaches.**

Front Microbiol. 2022 Jun 2;13:866873. doi: 10.3389/fmicb.2022.866873. eCollection 2022.

Khan Z(1)(2)(3)(4), Ualiyeva D(2)(5)(6), Amissah OB(1)(2), Sapkota S(1)(2)(3)(4), Hameed HMA(1)(2)(3)(4), Zhang T(1)(2)(3)(4).

Tuberculosis (TB), an infectious disease, has been a leading cause of morbidity and mortality for decades. The causative agent of TB is the Mycobacterium tuberculosis (Mtb) which can infects various parts of the body, mainly the lungs in pulmonary TB cases. Mycobacterium bovis Bacillus Calmette-Guerin (BCG) is the only approved vaccine for TB, but its efficiency to combat pulmonary TB is limited. Multidrug-resistant (MDR) TB and extensive drug-resistant (XDR) TB requires the evolution of more potent vaccines. Therefore, this research aims to generate a universal TB subunit vaccine using advanced immunoinformatics techniques. In generating a novel multiepitope subunit vaccine, we selected the conserved and experimentally confirmed antigens Rv0058, Rv0101, and Rv3343. After a rigorous evaluation, the top candidates from predicted Helper T-lymphocytes (HTL), Cytotoxic T-lymphocytes (CTL), and B-cell epitopes were considered potential vaccine candidates. Immunogenicity was enhanced by the addition of an adjuvant to the ultimate construct of the vaccine. B-cell epitopes predictions guaranteed the eventual induction of a humoral response. Thereafter, dynamics simulations and molecular docking validated the vaccine-receptor complex's stability and high affinity for the immune receptor TLR-3. Also, immune simulations revealed the significantly elevated levels of immunoglobulins such as IgM, cytokines such as interleukin-2, helper T (Th)

cells, and cytotoxic T-cell populations. These results agreed with the actual inflammatory response and showed rapid antigen clearance after manifold exposure. Finally, the E. coli K12 strain was confirmed via in-silico cloning for quality expression. Nevertheless, in vivo experiments should be performed to validate the safety of the proposed vaccine and its inherent ability to prevent TB infection.

DOI: 10.3389/fmicb.2022.866873
PMCID: PMC9201507
PMID: 35722321

Conflict of interest statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

19. **Effectiveness of the Novel Anti-TB Bedaquiline against Drug-Resistant TB in Africa: A Systematic Review of the Literature.**

Pathogens. 2022 Jun 1;11(6):636. doi: 10.3390/pathogens11060636.

Traoré AN(1), Rikhotso MC(1), Banda NT(1), Mashilo MS(1), Ngandu JPK(1), Mavumengwana V(2), Loxton AG(2), Kinnear C(2)(3), Potgieter N(1), Heysell S(4), Warren R(2).

BACKGROUND: In 2018, an estimated 10.0 million people contracted tuberculosis (TB), and 1.5 million died from it, including 1.25 million HIV-negative persons and 251,000 HIV-associated TB fatalities. Drug-resistant tuberculosis (DR-TB) is an important contributor to global TB mortality. Multi-drug-resistant TB (MDR-TB) is defined as TB resistant to at least isoniazid (INH) and rifampin (RMP), which are recommended by the WHO as essential drugs for treatment. OBJECTIVE: To investigate the effectiveness of bedaquiline addition to the treatment of drug-resistant TB infections on the African continent. METHODOLOGY: The search engine databases Medline, PubMed, Google Scholar, and Embase were used to obtain published data pertaining to DR-TB between 2012 and 2021 in Africa. Included studies had to document clinical characteristics at treatment initiation and outcomes at the end of treatment (i.e., success, failure, recurrence, loss to follow-up, and death). The included studies were used to conduct a meta-analysis. All data analysis and visualization were performed using the R programming environment. The log risk ratios and sample variances were calculated for DR-TB patients treated with BBQ monotherapy vs. BDQ and other drug therapy. To quantify heterogeneity among the included studies, random effect sizes were calculated.

RESULTS: A total of 16 studies in Africa from Mozambique (N = 1 study), Eswatini (N = 1 study), Democratic Republic of the Congo (N = 1 study), South Africa (N = 12 studies), and a multicenter study undertaken across Africa (N = 1 study) were included. In total, 22,368 individuals participated in the research studies. Among the patients, (55.2%; 12,350/22,368) were male while 9723/22,368 (44%) were female. Overall, (9%; 2033/22,368) of patients received BDQ monotherapy, while (88%; 19,630/22,368) patients received bedaquiline combined with other antibiotics. In total, (42%; 9465/22,368) of the patients were successfully treated. About (39%; 8653/22,368) of participants finished their therapy, meanwhile (5%; 1166/22,368) did not finish their therapy, while people (0.4%; 99/22,368) were lost to follow up. A total of (42%; 9265/22,368) patients died.
CONCLUSION: Very few studies on bedaquiline usage in DR-TB in Africa have been published to date. Bedaquiline has been shown to enhance DR-TB results in clinical studies and programmatic settings. Hence, the World Health Organization (WHO) has recommended that it be included in DR-TB regimens. However, in the current study limited improvement to DR-TB treatment results were observed using BDQ on the continent. Better in-country monitoring and reporting, as well as multi-country collaborative cohort studies of DR-TB, can expand the knowledge of bedaquiline usage and clinical impact, as well as the risks and benefits throughout the continent.

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PMCID: PMC9229213
PMID: 35745490

Conflict of interest statement: The authors declare no conflict of interest.

20. **The epidemiology of drug-resistant tuberculosis in Bulawayo and Matabeleland South provinces, Zimbabwe 2017.**

IJID Reg. 2022 Mar 10;3:37-43. doi: 10.1016/j.ijregi.2022.03.004. eCollection 2022 Jun.

Mugauri Dumisani H(1), Chirenda J(1), Juru T(1), Mugurungi O(2), Shambira G(1), Gombe N(1), Tshimanga M(1).

OBJECTIVE: To investigate determinants of drug resistance and treatment outcomes among patients with drug-resistant tuberculosis (DR-TB).
DESIGN: This was a cross-sectional study on patients diagnosed with DR-TB in Bulawayo and Matabeleland South provinces, 2015.
RESULTS: A total of 129 participants were identified. DR-TB patients were 3.4 times more likely to have been treated previously for sensitive TB (95% confidence interval 1.3-9.2). Approximately 88.5% of DR-TB patients were

diagnosed before completing the sensitive TB course and another 82.1% developed DR-TB within 6 months of completing sensitive TB treatment. The likelihood diminished with increasing time interval, becoming less likely at >12 months post-treatment. Most DR-TB patients (87.5%) were likely to have resided outside Zimbabwe and to have fallen ill there (85.2%). Overall, hearing loss was the most prevalent (70%) medication side effect experienced. Unfavourable interim treatment outcomes were high for patients <6 months on treatment (prevalence odds ratio 2.7, 95% CI 1.2-6.1), becoming 44% less likely after 18 months (95% CI 1.2-11.4).
CONCLUSIONS: The majority of DR-TB patients were diagnosed during sensitive TB treatment, suggesting missed DR-TB diagnosis or inadequate treatment. Delays in starting effective TB regimens negatively affect treatment outcomes. Drug sensitivity testing at diagnosis, patient monitoring, and enhanced adherence counselling are recommended.

DOI: 10.1016/j.ijregi.2022.03.004
PMCID: PMC9216256
PMID: 35755478

21. **Time trend prediction and spatial-temporal analysis of multidrug-resistant tuberculosis in Guizhou Province, China, during 2014-2020.**

BMC Infect Dis. 2022 Jun 7;22(1):525. doi: 10.1186/s12879-022-07499-9.

Yun W(1), Huijuan C(2), Long L(3), Xiaolong L(3), Aihua Z(1).

BACKGROUND: Guizhou is located in the southwest of China with high multidrug-resistant tuberculosis (MDR-TB) epidemic. To fight this disease, Guizhou provincial authorities have made efforts to establish MDR-TB service system and perform the strategies for active case finding since 2014. The expanded case finding starting from 2019 and COVID-19 pandemic may affect the cases distribution. Thus, this study aims to analyze MDR-TB epidemic status from 2014 to 2020 for the first time in Guizhou in order to guide control strategies.
METHODS: Data of notified MDR-TB cases were extracted from the National TB Surveillance System correspond to population information for each county of Guizhou from 2014 to 2020. The percentage change was calculated to quantify the change of cases from 2014 to 2020. Time trend and seasonality of case series were analyzed by a seasonal autoregressive integrated moving average (SARIMA) model. Spatial-temporal distribution at county-level was explored by spatial autocorrelation analysis and spatial-temporal scan statistic.
RESULTS: Guizhou has 9 prefectures and 88 counties. In this study, 1,666 notified MDR-TB cases were included from 2014-2020. The number of cases

increased yearly. Between 2014 and 2019, the percentage increase ranged from 6.7 to 21.0%. From 2019 to 2020, the percentage increase was 62.1%. The seasonal trend illustrated that most cases were observed during the autumn with the trough in February. Only in 2020, a peak admission was observed in June. This may be caused by COVID-19 pandemic restrictions being lifted until May 2020. The spatial-temporal heterogeneity revealed that over the years, most MDR-TB cases stably aggregated over four prefectures in the northwest, covering Bijie, Guiyang, Liupanshui and Zunyi. Three prefectures (Anshun, Tongren and Qiandongnan) only exhibited case clusters in 2020.
CONCLUSION: This study identified the upward trend with seasonality and spatial-temporal clusters of MDR-TB cases in Guizhou from 2014 to 2020. The fast rising of cases and different distribution from the past in 2020 were affected by the expanded case finding from 2019 and COVID-19. The results suggest that control efforts should target at high-risk periods and areas by prioritizing resources allocation to increase cases detection capacity and better access to treatment.

DOI: 10.1186/s12879-022-07499-9
PMCID: PMC9171477
PMID: 35672746 [Indexed for MEDLINE]

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

22. **Frequency and Management of Adverse Drug Reactions Among Drug-Resistant Tuberculosis Patients: Analysis From a Prospective Study.**

Front Pharmacol. 2022 Jun 2;13:883483. doi: 10.3389/fphar.2022.883483. eCollection 2022.

Massud A(1)(2), Syed Sulaiman SA(1), Ahmad N(3), Shafqat M(4), Chiau Ming L(5), Khan AH(1).

Drug-resistant tuberculosis (DR-TB) management is often linked with a higher rate of adverse drug reactions (ADRs) needing effective and timely management of these ADRs, which, if left untreated, may result in a higher rate of loss to follow-up of drug-resistant patients. Study objective: The study was aimed at prospectively identifying the nature, frequency, suspected drugs, and management approaches for ADRs along with risk factors of ADRs occurrence among DR-TB patients at Nishtar Medical University, Hospital, Multan, Pakistan. Materials and Methods: The prospective study included all the DR-TB patients enrolled for treatment from January 2016 to May 2017 at the study site. Patients were

evaluated for the treatment-induced ADRs as per standard criteria of the National Tuberculosis Program, Pakistan. Multivariate logistic regression was used to assess the independent variables associated with the occurrence of ADRs. Results: Out of 271 DR-TB patients included in the final analysis, it was observed that 55 patients (20.3%) experienced at least three ADRs. A total of 50 (18.5%) patients experienced zero adverse effects, while 15 (5.5%), 33 (12.2%), and 53 (19.6%) patients experienced one, two, and four ADRs, respectively. Gastrointestinal disturbances (66.7%), nervous system disorders (59.4%), and electrolyte disturbances (55.7%) remained the highest reported ADRs during therapy, followed by arthralgia (49.1%), ototoxicity (24%), pruritic reactions/rash (12.9%), dyspnoea (12.5%), and tinnitus (8.8%). Pulmonary cavitation at the baseline visit (p-value 0.001, OR 3.419; 95% CI (1.694-6.902) was significantly associated with the occurrence of ADRs among DR-TB patients. Conclusion: The frequency of ADRs was high among the study cohort; however, these were managed effectively. Patients with recognized risk factors for ADRs occurrence need continuous clinical management efforts.

DOI: 10.3389/fphar.2022.883483
PMCID: PMC9211428
PMID: 35747749

Conflict of interest statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

23. **An effective nano drug delivery and combination therapy for the treatment of Tuberculosis.**

Sci Rep. 2022 Jun 10;12(1):9591. doi: 10.1038/s41598-022-13682-4.

Sheikhpour M(1)(2), Delorme V(3), Kasaeian A(4), Amiri V(5), Masoumi M(5), Sadeghinia M(6), Ebrahimzadeh N(5), Maleki M(5), Pourazar S(5).

Drug resistance in tuberculosis is exacerbating the threat this disease is posing to human beings. Antibiotics that were once effective against the causative agent, Mycobacterium tuberculosis (Mtb), are now no longer usable against multi- and extensively drug-resistant strains of this pathogen. To address this issue, new drug combinations and novel methods for targeted drug delivery could be of considerable value. In addition, studies have shown that the use of the antidepressant drug fluoxetine, a serotonin reuptake inhibitor, can be useful in the treatment of infectious diseases, including bacterial infections. In this study, an isoniazid and fluoxetine-conjugated multi-walled

carbon nanotube nanofluid were designed to increase drug delivery efficiency alongside eliminating drug resistance in vitro. The prepared nanofluid was tested against Mtb. Expression levels of inhA and katG mRNAs were detected by Real-time PCR. ELISA was applied to measure levels of cytokine secretion (TNF-α, and IL-6) from infected macrophages treated with the nano delivery system. The results showed that these nano-drug delivery systems are effective for fluoxetine at far lower doses than for free drugs. Fluoxetine also has an additive effect on the effect of isoniazid, and their concomitant use in the delivery system can have significant effects in treating infection of all clinical strains of Mtb. In addition, it was found that the expression of isoniazid resistance genes, including inhA, katG, and the secretion of cytokines TNFα and IL6 under the influence of this drug delivery system is well regulated. It was shown that the drug conjugation can improve the antibacterial activity of them in all strains and these two drugs have an additive effect on each other both in free and conjugated forms. This nano-drug delivery method combined with host targeted molecules could be a game-changer in the development of a new generation of antibiotics that have high therapeutic efficiencies, low side effects, and the potential to overcome the problem of drug resistance.

DOI: 10.1038/s41598-022-13682-4
PMCID: PMC9185718
PMID: 35688860 [Indexed for MEDLINE]

Conflict of interest statement: The authors declare no competing interests.

24. **Epidemiological and laboratory characteristics of multidrug-resistant tuberculosis patients in Bhutan, 2015-2019.**

IJID Reg. 2022 Apr 29;3:228-233. doi: 10.1016/j.ijregi.2022.04.012. eCollection 2022 Jun.

Adhikari L(1), Wangchuk S(1), Bhujel P(1), Zangmo S(1), Lhaden P(1), Dorji U(1), Tshering K(1).

BACKGROUND: Bhutan is no exception to the rising global threat of drug resistance tuberculosis (TB), particularly multidrug-resistant (MDR) TB. Although drug resistance surveillance has been carried out in Bhutan since 2010, limited analysis reports are available. Therefore, we looked at data from 2015-2019 to understand patient characteristics.
METHOD: To obtain data for MDR-TB from the past 5 years, we looked at manual registers and laboratory worksheets for all samples received at National TB

Reference Laboratory. Epidemiological factors and laboratory variables were analyzed using descriptive statistics.
RESULT: Among 304 patients with MDR-TB, 85.20% (n=259) are new cases with no previous history of treatment. Those aged 16-25 years from both genders are affected more (46.05%, n=140) than other age groups. The majority (94.62%, n=264) of rifampicin resistance was found in the MUT 3 rpoB gene. For Isoniazid, 97.13% (n=271) resistance was seen in the MUT1 band of the katG gene.
CONCLUSION: A high number of MDR-TB cases among new patients and little variation in the resistance band pattern over 5 years could indicate uncontrolled ongoing transmission. Whole-genome sequencing for the samples is required to further understand the epidemiology of the resistance pattern.

DOI: 10.1016/j.ijregi.2022.04.012
PMCID: PMC9216444
PMID: 35755459

Conflict of interest statement: No conflict of interest to declare.

25. **Treatment outcomes of multidrug-resistant tuberculosis with chronic kidney/liver disease.**

Eur Respir J. 2022 Jun 16:2200930. doi: 10.1183/13993003.00930-2022. Online ahead of print.

Chung C(1)(2), Shin JE(1)(2), Jeon D(3), Kang H(4), Yim JJ(5), Jo KW(1), Shim TS(6).

DOI: 10.1183/13993003.00930-2022
PMID: 35710263

26. **Male reproductive hormones in patients treated with pretomanid.**

Int J Tuberc Lung Dis. 2022 Jun 1;26(6):558-565. doi: 10.5588/ijtld.21.0654.

Boekelheide K(1), Olugbosi M(2), Nedelman J(3), Everitt D(3), Smith E(3), Betteridge M(3), Sun E(3), Spigelman M(3).

BACKGROUND: Pretomanid (Pa) is a nitroimidazole-class drug recently approved by the US Food and Drug Administration and other regulatory authorities as part of a regimen for treating highly drug-resistant pulmonary Mycobacterium tuberculosis infections. Studies in rodents identified the testis as a target organ of concern, which led to monitoring of reproductive hormones in >800 male

patients enrolled in four clinical trials of Pa-containing regimens and the HRZE (isoniazid+rifampin+pyrazinamide+ethambutol) control regimen.METHODS: Serum hormone levels relevant to male reproductive health - follicle stimulating hormone (FSH), luteinizing hormone (LH), inhibin B (InhB) and total testosterone (T) - from the four clinical trials were summarized numerically and analyzed by repeated-measures modeling.RESULTS: Hormone levels generally behaved similarly in Pa-containing and HRZE arms. Relative to baseline, serum T and InhB levels generally increased at the end of treatment and follow-up. FSH and LH levels were variable, but were generally at or below baseline levels by follow-up. Before treatment, many patients were borderline hypogonadal, with T levels near the lower limits of the normal range.CONCLUSION: Changes in male hormones in four clinical trials studying patients with TB indicate that Pa-containing treatment was not associated with testicular toxicity but rather led to improvement in the underlying hypogonadism.

DOI: 10.5588/ijtld.21.0654
PMCID: PMC9165738
PMID: 35650700 [Indexed for MEDLINE]

Conflict of interest statement: Conflicts of interest: KB has been a paid consultant to TB Alliance since 2013, providing his expertise in male reproductive tract toxicity and the clinical assessment of male reproductive tract function. He received no compensation for his effort in performing the background research, data integration, and writing of this manuscript.

27. **Integrating hepatitis C treatment into multidrug-resistant TB care.**

Public Health Action. 2022 Jun 21;12(2):96-101. doi: 10.5588/pha.22.0002.

Kirakosyan O(1), Melikyan N(1)(2), Falcao J(2), Khachatryan N(1)(3), Atshemyan H(1), Oganezova I(1), Aznauryan A(1), Yeghiazaryan L(3), Sargsyants N(1)(4), Hayrapetyan A(3), Balkan S(5), Hewison C(5), Huerga H(2).

BACKGROUND: Direct-acting antivirals (DAAs) are not widely used for patients with chronic hepatitis C virus (HCV) infection and multidrug- or rifampicin-resistant TB (MDR/RR-TB). We describe the implementation aspects of a new integrated model of care in Armenia and the perceptions of the healthcare staff and patients.
METHODS: We used qualitative methods, including a desktop review and semi-structured individual interviews with healthcare staff and with patients receiving HCV and MDR/RR-TB treatment.
RESULTS: The new integrated model resulted in simplified management of HCV and MDR/RR-TB at public TB facilities. Training on HCV was provided for TB clinic staff. All MDR/RR-TB patients were systematically offered HCV testing and those

diagnosed with HCV, offered treatment with DAAs. Treatment monitoring was performed by TB staff in coordination with a hepatologist. The staff interviewed had a positive opinion of the new model. They suggested that additional training should be provided. Most patients were fully satisfied with the care received. Some were concerned about the increased pill burden.
CONCLUSION: Integrating HCV treatment into MDR/ RR-TB care was feasible and appreciated by patients and staff. This new model facilitated HCV diagnosis and treatment among people with MDR/RR-TB. Our results encourage piloting this model in other settings.

DOI: 10.5588/pha.22.0002
PMCID: PMC9176196
PMID: 35734011

28. **Pharmacokinetics of standard versus high-dose isoniazid for treatment of multidrug-resistant tuberculosis.**

J Antimicrob Chemother. 2022 Jun 9:dkac188. doi: 10.1093/jac/dkac188. Online ahead of print.

Gausi K(1), Chirehwa M(1), Ignatius EH(2), Court R(1)(3), Sun X(4), Moran L(5), Hafner R(6), Wiesner L(1), Rosenkranz SL(7), de Jager V(8), de Vries N(9), Harding J(10), Gumbo T(11), Swindells S(12), Diacon A(8), Dooley KE(2), McIlleron H(1)(3), Denti P(1).

BACKGROUND: The WHO-endorsed shorter-course regimen for MDR-TB includes high-dose isoniazid. The pharmacokinetics of high-dose isoniazid within MDR-TB regimens has not been well described.
OBJECTIVES: To characterize isoniazid pharmacokinetics at 5-15 mg/kg as monotherapy or as part of the MDR-TB treatment regimen.
METHODS: We used non-linear mixed-effects modelling to evaluate the combined data from INHindsight, a 7 day early bactericidal activity study with isoniazid monotherapy, and PODRtb, an observational study of patients on MDR-TB treatment including terizidone, pyrazinamide, moxifloxacin, kanamycin, ethionamide and/or isoniazid.
RESULTS: A total of 58 and 103 participants from the INHindsight and PODRtb studies, respectively, were included in the analysis. A two-compartment model with hepatic elimination best described the data. N-acetyltransferase 2 (NAT2) genotype caused multi-modal clearance, and saturable first-pass was observed beyond 10 mg/kg dosing. Saturable isoniazid kinetics predicted an increased exposure of approximately 50% beyond linearity at 20 mg/kg dosing. Participants treated with the MDR-TB regimen had a 65.6% lower AUC compared with participants

on monotherapy. Ethionamide co-administration was associated with a 29% increase in isoniazid AUC.
CONCLUSIONS: Markedly lower isoniazid exposures were observed in participants on combination MDR-TB treatment compared with monotherapy. Isoniazid displays saturable kinetics at doses >10 mg/kg. The safety implications of these phenomena remain unclear.

DOI: 10.1093/jac/dkac188
PMID: 35678468

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

Lancet Glob Health. 2022 Jul;10(7):e942-e943. doi: 10.1016/S2214-109X(22)00200-5. Epub 2022 May 18.

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

DOI: 10.1016/S2214-109X(22)00200-5
PMID: 35597250 [Indexed for MEDLINE]

Conflict of interest statement: We declare no competing interests.

30. **Discovery and preclinical profile of sudapyridine (WX-081), a novel anti-tuberculosis agent.**

Bioorg Med Chem Lett. 2022 Sep 1;71:128824. doi: 10.1016/j.bmcl.2022.128824. Epub 2022 May 27.

Huang Z(1), Luo W(1), Xu D(2), Guo F(2), Yang M(2), Zhu Y(2), Shen L(2), Chen S(2), Tang D(1), Li L(3), Li Y(3), Wang B(4), Franzblau SG(5), Ding CZ(6).

Multidrug resistant tuberculosis (MDR-TB) remains a major human health challenge. Bedaquiline was approved in 2012 by the US FDA, and listed by WHO as a treatment for multidrug-resistant tuberculosis (MDR-TB) in 2018. However, the side effects of bedaquiline including the risk of unexplained mortality, QTc prolongation and hepatotoxicity limit its wide clinical use. Based on bedaquiline, we describe herein discovery and development of a novel diarylpyridine series, which led to identification of WX-081 (sudapyridine, 21l). It displayed excellent anti-mycobacterial activity against M. tuberculosis

H37Rv in vitro and in vivo and low cytotoxicity; additionally WX-081 had excellent pharmacokinetic parameters in animals, better lung exposure and lower QTc prolongation potential compared to bedaquiline. WX-081 is currently under clinical phase II development (NCT04608955).

DOI: 10.1016/j.bmcl.2022.128824
PMID: 35636648 [Indexed for MEDLINE]

31. **Discovery of new riminophenazine analogues as antimycobacterial agents against drug-resistant Mycobacterium tuberculosis.**

Bioorg Chem. 2022 Jun 7:105929. doi: 10.1016/j.bioorg.2022.105929. Online ahead of print.

Zhao X(1), Mei Y(1), Guo Z(1), Si S(1), Ma X(1), Li Y(2), Li Y(3), Song D(1).

Twenty-three new riminophenazine and pyrido[3,2-b]quinoxaline derivatives were prepared and examined for their antimycobacterial activities against Mycobacterium marinum and Mycobacterium tuberculosis H37Rv, taking clofazimine (1) as the lead. Structure-activity relationship (SAR) analysis revealed that the introduction of a heterocycle or diethylamine substituted benzene moiety on the N-5 atom might be beneficial for activity. The most potent compound 7m also displayed enhanced activity against wild-type as well as multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB clinical isolates, with the MICs ranging from 0.08 to 1.25 μg/mL, especially effective toward strain M20A507, resistant to 1. Further mechanism study indicated that its anti-TB activity was independent of cell membrane disruption, but related to NDH-2 reduction and the resulting high ROS production. Our study provides instructive guidance for the further development of clofazimine derivatives into promising antimicrobial agents against MDR and XDR TB.

DOI: 10.1016/j.bioorg.2022.105929
PMID: 35701239

32. **A multidrug efflux protein in Mycobacterium tuberculosis; tap as a potential drug target for drug repurposing.**

Comput Biol Med. 2022 Jul;146:105607. doi: 10.1016/j.compbiomed.2022.105607. Epub 2022 May 16.

Dwivedi M(1), Mukhopadhyay S(2), Yadav S(3), Dubey KD(3).

Tuberculosis (TB) is a serious communicative disease caused by Mycobacterium tuberculosis. Although there are vaccines and drugs available to treat the disease, they are not efficient, moreover, multidrug-resistant TB (MDR-TB) become a major hurdle in its therapy. These MDR strains utilize the multidrug efflux pump as a decisive weapon to fight against antitubercular drugs. Tap membrane protein was observed as a crucial multidrug efflux pump in M. tuberculosis and its critical implication in MDR-MTB development makes it an effective drug target. In the present study, we have utilized various in silico approaches to predict the applicability of FDA-approved ion channel inhibitors and blockers as therapeutic leads against Tuberculosis by targeting multidrug efflux protein; Tap in MTB. Tap protein structure is predicted by Phyre2 server followed by model refinement, validation, physio-chemical catheterization and target prediction. Further, the interaction between Tap protein and ligands were analysed by molecular docking and MD simulation run of 100 ns. Based on implication and compatibility, 18 FDA-approved ion channel inhibitors and blockers are selected as a ligand against the Tap protein and eventually observed five ligands; Glimepiride, Flecainide, Flupiritine, Nimodipine and Amlodipine as promising compounds which have exhibited the significant stable interaction with Tap protein and are proposed to modulate or interfere with its activity. These compounds illustrated the substantial docking score and total binding enthalpy more than -7 kcal/mol and -42 kcal/mol respectively which implies that the selected FDA-approved compounds can spontaneously interact with the Tap protein to modulate its function. This study proposed Tap protein as a prominent drug target in MTB and investigated compounds that show considerable interaction with the Tap protein as potential therapeutic molecules. These interactions may lead to modulating or inhibit the activity of drug efflux protein thereby making MTB susceptible to antitubercular drugs.

DOI: 10.1016/j.compbiomed.2022.105607
PMID: 35617724 [Indexed for MEDLINE]

33. TB-PRACTECAL: study protocol for a randomised, controlled, open-label, phase II-III trial to evaluate the safety and efficacy of regimens containing bedaquiline and pretomanid for the treatment of adult patients with pulmonary multidrug-resistant tuberculosis.

Trials. 2022 Jun 13;23(1):484. doi: 10.1186/s13063-022-06331-8.

Berry C(1), du Cros P(2)(3), Fielding K(4), Gajewski S(5), Kazounis E(2), McHugh

TD(6), Merle C(7), Motta I(2), Moore DAJ(8), Nyang'wa BT(9).

BACKGROUND: Globally rifampicin-resistant tuberculosis disease affects around 460,000 people each year. Currently recommended regimens are 9-24 months duration, have poor efficacy and carry significant toxicity. A shorter, less toxic and more efficacious regimen would improve outcomes for people with rifampicin-resistant tuberculosis.
METHODS: TB-PRACTECAL is an open-label, randomised, controlled, phase II/III non-inferiority trial evaluating the safety and efficacy of 24-week regimens containing bedaquiline and pretomanid to treat rifampicin-resistant tuberculosis. Conducted in Uzbekistan, South Africa and Belarus, patients aged 15 and above with rifampicin-resistant pulmonary tuberculosis and requiring a new course of therapy were eligible for inclusion irrespective of HIV status. In the first stage, equivalent to a phase IIB trial, patients were randomly assigned one of four regimens, stratified by site. Investigational regimens include oral bedaquiline, pretomanid and linezolid. Additionally, two of the regimens also included moxifloxacin (arm 1) and clofazimine (arm 2) respectively. Treatment was administered under direct observation for 24 weeks in investigational arms and 36 to 96 weeks in the standard of care arm. The second stage of the study was equivalent to a phase III trial, investigating the safety and efficacy of the most promising regimen/s. The primary outcome was the percentage of unfavourable outcomes at 72 weeks post-randomisation. This was a composite of early treatment discontinuation, treatment failure, recurrence, lost-to-follow-up and death. The study is being conducted in accordance with ICH-GCP and full ethical approval was obtained from Médecins sans Frontières ethical review board, London School of Hygiene and Tropical Medicine ethical review board as well as ERBs and regulatory authorities at each site.
DISCUSSION: TB-PRACTECAL is an ambitious trial using adaptive design to accelerate regimen assessment and bring novel treatments that are effective and safe to patients quicker. The trial took a patient-centred approach, adapting to best practice guidelines throughout recruitment. The implementation faced significant challenges from the COVID-19 pandemic. The trial was terminated early for efficacy on the advice of the DSMB and will report on data collected up to the end of recruitment and, additionally, the planned final analysis at 72 weeks after the end of recruitment.
TRIAL REGISTRATION: Clinicaltrials.gov NCT02589782. Registered on 28 October 2015.

DOI: 10.1186/s13063-022-06331-8
PMCID: PMC9190445
PMID: 35698158 [Indexed for MEDLINE]

Conflict of interest statement: Philipp du Cros has received funding from TB Alliance for a project to analyse introduction and scale up of pretomanid and the NIX-TB regimen. Philipp du Cros is a member of the rGLC WPRO region. CM is currently staff members of the World Health Organization; the authors alone are responsible for the views expressed in this publication and they do not necessarily represent the decisions, policy or views of the WHONo other authors had conflicts to declare.

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

Int J Infect Dis. 2022 Aug;121:47-54. doi: 10.1016/j.ijid.2022.04.061. Epub 2022 May 4.

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

OBJECTIVES: To evaluate the performance of nucleotide matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF-MS) in predicting the drug resistance of Mycobacterium tuberculosis.
METHODS: A total of 115 rifampin-resistant and 53 rifampin-susceptible tuberculosis (TB) clinical isolates were randomly selected from TB strains stored at -80℃ in the clinical laboratory of Shanghai Pulmonary Hospital. Nucleotide MALDI-TOF-MS was performed to predict the drug resistance using phenotypic susceptibility as the gold standard.
RESULTS: The overall assay sensitivities and specificities of nucleotide MALDI-TOF-MS were 92.2% and 100.0% for rifampin, 90.9% and 98.6% for isoniazid, 71.4% and 81.2% for ethambutol, 85.1% and 93.1% for streptomycin, 94.0% and 100.0% for amikacin, 77.8% and 99.3% for kanamycin, 75.0% and 93.3% for ofloxacin, and 75.0% and 93.3% for moxifloxacin. The concordances between nucleotide MALDI-TOF-MS antimicrobial susceptibility testing (AST) and phenotypic AST were 94.6% (rifampin), 90.1% (isoniazid), 79.2% (ethambutol), 89.9% (streptomycin), 99.4% (amikacin), 97.0% (kanamycin), 88.1% (ofloxacin), and 88.0% (moxifloxacin).
CONCLUSION: Nucleotide MALDI-TOF-MS could be a promising tool for rapid detection of Mycobacterium tuberculosis drug sensitivity to rifampin, isoniazid, ethambutol, streptomycin, amikacin, kanamycin, ofloxacin, and moxifloxacin.

DOI: 10.1016/j.ijid.2022.04.061
PMID: 35523300 [Indexed for MEDLINE]

Conflict of interest statement: CONFLICTS OF INTEREST The authors have no competing interests to declare.

35. **Increased linezolid plasma concentrations are associated with the development of severe toxicity in MDR-TB treatment.**

Clin Infect Dis. 2022 Jun 19:ciac485. doi: 10.1093/cid/ciac485. Online ahead of print.

Eimer J(1), Fréchet-Jachym M(2), Le Dû D(2), Caumes E(3), El-Helali N(4), Marigot-Outtandy D(2)(5), Mechai F(6), Peytavin G(7), Pourcher V(3), Rioux C(8), Yazdanpanah Y(8), Robert J(1)(9), Guglielmetti L(1)(9); LZDM group.

BACKGROUND: Treatment of multidrug-resistant tuberculosis (MDR-TB) with linezolid is characterized by high rates of adverse events. Evidence on therapeutic drug monitoring to predict drug toxicity is scarce. This study aimed to evaluate the association of linezolid trough concentrations with severe toxicity.
METHODS: We retrospectively assessed consecutive patients started on linezolid for MDR-TB between 2011 and 2017. The primary outcome was severe mitochondrial toxicity (SMT) due to linezolid, defined as neurotoxicity or myelotoxicity leading to drug discontinuation. The impact of plasma linezolid trough concentrations >2 mg/L was assessed in multivariate Cox proportional hazards models including time-varying covariates.
RESULTS: SMT occurred in 57 of 146 included patients (39%) at an incidence rate of 0.38 per person-year (95%CI 0.30-0.49). A maximum linezolid trough concentration >2 mg/L was detected in 52 patients (35.6%), while the mean trough concentration was >2 mg/L in 22 (15%). The adjusted hazard ratio for SMT was 2.35 (95%CI 1.26-4.38, p = 0.01) in patients with a mean trough concentration >2 mg/L and 2.63 (95%CI 1.55-4.47, p < 0.01) for SMT after the first detection of a trough concentration >2 mg/L. In an exploratory analysis, higher maximum trough concentrations were dose-dependently associated with toxicity, while lowering of elevated trough concentrations did not restore baseline risk.
CONCLUSION: Linezolid trough concentrations >2 mg/L are strongly associated with the development of severe treatment-emergent toxicity in patients treated for MDR-TB. Pending further prospective evidence, an individual risk-benefit assessment on the continuation of linezolid treatment is warranted in any patient with trough concentrations above 2 mg/L.

DOI: 10.1093/cid/ciac485
PMID: 35717636

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

Eur J Med Chem. 2022 Aug 5;238:114454. doi: 10.1016/j.ejmech.2022.114454. Epub 2022 May 13.

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

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

DOI: 10.1016/j.ejmech.2022.114454
PMID: 35597009 [Indexed for MEDLINE]

37. **Proposed Linezolid Dosing Strategies to Minimize Adverse Events for Treatment of Extensively Drug-Resistant Tuberculosis.**

Clin Infect Dis. 2022 May 30;74(10):1736-1747. doi: 10.1093/cid/ciab699.

Imperial MZ(1), Nedelman JR(2), Conradie F(3), Savic RM(1).

BACKGROUND: We evaluated Nix-TB trial data (NCT02333799, N = 109) to provide dosing recommendations to potentially minimize linezolid toxicity in patients with extensively drug-resistant tuberculosis. .
METHODS: A pharmacokinetic model and toxicodynamic models for peripheral neuropathy, hemoglobin, and platelets were developed. Simulations compared safety outcomes for daily linezolid of 1200 and 600 mg, with and without dose adjustments for toxicity. Severe neuropathy was based on symptom scores from the Brief Peripheral Neuropathy Screen. Severe anemia and thrombocytopenia were defined as ≥ grade 3 adverse events according to the NIAID Division of Microbiology and Infectious Disease Adult Toxicity table.
RESULTS: Predicted concentration-time profiles were a major predictor in all toxicodynamic models. Simulations showed higher percentages of patients with severe neuropathy (median, 19%; 90% confidence interval [CI], 17%-22% vs 5%, 4%-7%) and severe anemia (15%, 12%-17% vs 1%, 0%-2%) between 1200 and 600 mg daily linezolid. No differences in severe thrombocytopenia were observed (median, <1% for both daily doses). Generally, neuropathy occurred after 3 to 6 months of treatment and, with protocol-specified management, reversed within 15 months after onset. Simulations indicated that a >10% decrease in hemoglobin level after 4 weeks of treatment would have maximum sensitivity (82%) and specificity (84%) for predicting severe anemia. Reducing the dose from 1200 to 600 mg triggered by this marker may prevent 60% (90% CI, 45%-72%) of severe anemia.
CONCLUSIONS: Simple neuropathy symptom and hemoglobin monitoring may guide linezolid dosing to avoid toxicities, but prospective testing is needed to confirm the benefit-to-risk ratio.

DOI: 10.1093/cid/ciab699
PMCID: PMC9155613
PMID: 34604901 [Indexed for MEDLINE]

38. **Virtually screened novel sulfathiazole derivatives as a potential drug candidate for methicillin-resistant Staphylococcus aureus and multidrug-resistant tuberculosis.**

J Biomol Struct Dyn. 2022 May 28:1-10. doi: 10.1080/07391102.2022.2079002. Online ahead of print.

Nagendran S(1), Balasubramaniyan S(2), Irfan N(3).

Methicillin-resistant Staphylococcus aureus (MRSA) and multidrug-resistant

tuberculosis (MDR-TB) is a leading cause of severe hospital and infection-related morbidity and mortality in the general population. There is a critical need for dynamic, powerful medication candidates to combat MRSA and MDR-TB infections in this specific setting. As a result, the current research focuses on the development of novel sulfathiazole derivative compounds that could be used as anti-MRSA and anti-MDR-TB agents. Virtual screening approaches were used to identify the potential lead sulfathiazole derivatives with the help of BIOVIA Discovery Studio 2017 software. In this in silico study, 10 novel sulfathiazole derivatives were virtually screened from 74 designed compounds. These 10 compounds had the best predictive docking scores in MRSA and MDR-TB receptors and were then put through a molecular dynamics simulation to explain protein stability, ligand characteristics and protein-ligand interactions. The Lipinski rule and ADMET prediction results also suggested that 11 compounds (mol-12, mol-22, mol-23, mol-28, mol-30, mol-32, mol-34, mol-35, mol-45 and mol-47) have strong drug similarity features. Our findings imply that the 10 novel sulfathiazole compounds studied could be viable new therapeutic leads for MRSA and MDR-TB.Communicated by Ramaswamy H. Sarma.

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PMID: 35635120

39. **Agreement between CBNAAT, liquid culture and line probe assay for detection of Mycobacterium tuberculosis and anti-tubercular drug resistance in extrapulmonary samples.**

Indian J Med Microbiol. 2022 Jun 13:S0255-0857(22)00094-9. doi: 10.1016/j.ijmmb.2022.05.013. Online ahead of print.

Jain P(1), Singh U(1), Kumar V(1), Ratnam R(1), Jain A(2).

PURPOSE: Cartridge based nucleic acid amplification test (CBNAAT) has been endorsed by the WHO as the screening test for diagnosing extrapulmonary tuberculosis (EPTB). In the present study we report the agreement between CBNAAT (Xpert MTB/RIF), liquid culture (LC) and line probe assay (LPA) for diagnosis of Mycobacterium tuberculosis and detection of drug resistance among EPTB cases.
METHODS: The EP samples were subjected to CBNAAT (Xpert MTB/RIF, Cepheid, USA) and wherever possible, to LC (MGIT 960, Becton Dickinson, USA) followed sequentially by first line and second line-LPA (FL-LPA, SL-LPA, Hain Lifescience, Germany) on the isolates.
RESULTS: Total 566/4080 (13.9%) EP samples were detected positive for M. tuberculosis on CBNAAT. Aspirates from lymph nodes were most often positive (11/30; 36.6%), followed by pus (240/873; 27.5%) and CSF samples (166/104; 15.8%). The detection of M. tuberculosis was more in adults than children except

in tissue biopsy samples. Rifampicin resistance was also higher among adults except CSF in which resistance was more in children. Total 185 of 566 (32.7%) CBNAAT positive and 770 of 3510 (21.9%) CBNAAT negative samples could be cultured of which 110/185 (59.4%) and 33/770 (4.3%) respectively turned positive. FL-LPA and SL-LPA of 143 culture isolates showed that 27 isolates had drug resistance, of which 3 (2.1%) were XDR, 11 (7.7%) were Pre-XDR (FQ) and 13 (9.1%) were MDR. Of these 27 resistant isolates, 12 were negative by CBNAAT and two were mislabeled as Rifampicin sensitive or indeterminate based on the unique RpoB gene mutation patterns on LPA. The positive and negative agreements between LC and CBNAAT for detection of M. tuberculosis were 67.1% and 92.7% respectively and between LPA and CBNAAT for rifampicin resistance detection were 98.9% and 92.9% respectively.
CONCLUSIONS: For EPTB, CBNAAT should be accompanied with LC wherever possible irrespective of the CBNAAT result.

DOI: 10.1016/j.ijmmb.2022.05.013
PMID: 35710480

Conflict of interest statement: Conflict of interest None.

40. **24 loci MIRU-VNTR analysis and pattern of drug resistance in pre-extensively drug resistant pulmonary tuberculosis in Bangladesh.**

Infect Genet Evol. 2022 Aug;102:105304. doi: 10.1016/j.meegid.2022.105304. Epub 2022 May 18.

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

Phylogenetic diversity and distinct phylogeographic distribution of Mycobacterium tuberculosis (MTB) contribute to regional differences in drug resistance. The emergence of pre-extensively drug resistant tuberculosis (Pre-XDR-TB) becomes obstacles to achieve End TB strategy in Bangladesh. This cross-sectional study was conducted to identify the strains of different lineages of MTB, their variations of distribution among Pre-XDR-TB cases and to observe the linkage of particular strains of MTB with drug resistance. A total of 33 Pre-XDR-TB isolates were enrolled in this study. All isolates were confirmed as MTB by MPT 64 antigen detection and genotyped by 24 loci Mycobacterial Interspersed Repetitive Unit-Variable Number of Tandem Repeats (MIRU-VNTR) analysis. Drug resistance was detected by second line Line probe assay (LPA). Beijing was the predominant strain 16 (48.48%), followed by Delhi/CAS 5(15.15%), LAM 4 (12.12%) and Harlem 3(9.10%), EAI 2(6.06%), Cameroon

2(6.06%) and NEW-1 1(3.03%). There were 31 different genotypes consisting of 2 clusters and 29 singletons. All the clustered strains were belonged to Beijing lineage. Recent transmission occurred manly by Beijing strains, showed low transmission rate (12.1%). Of 33 isolates 30(90.90%) were Fluoroquinolones resistant, the mutations involved was Asp94Gly in gyr A MUT 3C gene 13(39.39%) in quinolone resistance determining region (QRDR) followed by 11 (33.33%) in gyr A MUT 1. Three (9.10%) isolates showed resistant to injectable 2nd line drugs and all mutation occurs in G1484T of rrs MUT 2. Beijing lineage was predominant in treatment failure and relapse cases. Levofloxacin was resistant to all Pre-XDR-TB cases, but moxifloxacin showed low level resistance. QUB 26 was the most discriminatory locus (0.85) among 24 loci whereas MIRU 2 was the least (0.03). 24 loci MIRU-VNTR analysis shows high discriminatory index (0.71), found to be powerful tool for genotyping of Pre-XDR-TB, which is the first study in Bangladesh that enhanced the current TB control policy.

DOI: 10.1016/j.meegid.2022.105304
PMID: 35595025 [Indexed for MEDLINE]

41. **Prediction of different interventions on the burden of drug-resistant tuberculosis in China: a dynamic modelling study.**

J Glob Antimicrob Resist. 2022 Jun;29:323-330. doi: 10.1016/j.jgar.2022.03.018. Epub 2022 Mar 26.

Xu A(1), Wen ZX(1), Wang Y(1), Wang WB(2).

BACKGROUND: Tuberculosis (TB) is one of the top 10 causes of death worldwide. The World Health Organization adopted the 'End TB Strategy' to end the global TB epidemic by 2035. However, achieving this goal will be difficult using current measures.
METHODS: A Susceptible-Exposed-Infectious-Recovered (SEIR) model that distinguishes drug-sensitive (DS) and drug-resistant (DR) TB in the entire Chinese population was established. Goodness-of-fit tests and sensitivity analyses were used to assess model performance. Predictive analysis was performed to assess the effect of different prevention and control strategies on DR-TB.
RESULTS: We used parameter fitting to determine the basic reproduction number of the model as R0 = 0.6993. The predictive analysis led to two major projections that can achieve the goal by 2035. First, if the progression rate of latently infected people reaches 10%, then there will be 92.2% fewer cases than in 2015. Second, if the cure rate of DR-TB increases to 40%, then there will be 91.5% fewer cases than in 2015. A combination of five interventions could lead to

earlier achievement of the 2035 target.
CONCLUSION: We found that reducing the probability of transmission and the rate of disease progression in patients with DR-TB and improving treatment compliance and the cure rate of patients with DR-TB can contribute to attaining the goal of the End TB Strategy.

DOI: 10.1016/j.jgar.2022.03.018
PMID: 35351676 [Indexed for MEDLINE]

42. **Frequency of rpoB, katG, and inhA Gene Polymorphisms Associated with Multidrug-Resistant Mycobacterium tuberculosis Complex Isolates among Ethiopian TB Patients: A Systematic Review.**

Interdiscip Perspect Infect Dis. 2022 Jun 16;2022:1967675. doi: 10.1155/2022/1967675. eCollection 2022.

Seid A(1)(2), Berhane N(1), Nureddin S(3).

Tuberculosis (TB) is one of the top 10 causes of mortality and the first killer among infectious diseases of poverty (IDoPs) worldwide. It disproportionately affects on-third of the world's low-income countries including Ethiopia. One of the factors driving the TB epidemic is the global rise of MDR/XDR-TB and their low detection affect the global TB control progress. Recently, the resistance-associated genetic mutations in MTBC known to confer drug resistance have been detected by rapid molecular diagnostic tests and sequencing methods. In this article, the published literature searched by PubMed database from 2010 to 2021 and English language were considered. The aim of this systematic review was to assess the prevalence of the most common rpoB, katG, and inhA gene mutations associated with multidrug resistance in MTBC clinical strains among TB patients in Ethiopia. Though 22 studies met our eligibility criteria, only 6 studies were included in the final analysis. Using the molecular GenoType MTBDRplus and MTBDRsl line probe assay and sequencing procedures, a total of 932 culture-positive MTBC isolates were examined to determine RIF, INH, and MDR-TB resistance patterns along with rpoB, katG, and inhA gene mutation analysis. As a result, among the genotypically tested MTBC isolates, 119 (12.77%), 83 (8.91%), and 73 (7.32%) isolates were INH, RIF, and MDR-TB resistant, respectively. In any RIF-resistant MTBC strains, the most common single point mutations were in codon 531 (S531L) followed by codon 526 (H526Y) of the rpoB gene. Besides, the most common mutations in any INH-resistant MTBC were strains observed at codon 315 (S315T) and WT probe in the katG gene and at codon C15T and WT1 probe in the inhA promoter region. Detection of resistance allele in rpoB, KatG, and inhA genes for RIF and INH could serve as a marker for MDR-TB strains. Tracking the

most common S531L, S315T, and C15T mutations in rpoB, katG, and inhA genes among RIF- and INH-resistant isolates would be valuable in TB diagnostics and treatment regimens, and could reduce the development and risk of MDR/XDR-TB drug-resistance patterns.

DOI: 10.1155/2022/1967675
PMCID: PMC9225881
PMID: 35757683

Conflict of interest statement: The authors declare that they have no conflicts of interest.

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

Anal Chem. 2022 Jun 7;94(22):7918-7927. doi: 10.1021/acs.analchem.2c00723. Epub 2022 May 20.

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

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

DOI: 10.1021/acs.analchem.2c00723
PMID: 35594337 [Indexed for MEDLINE]

44. **Predominance of the East-Asian Beijing genotype in a Mycobacterium tuberculosis drug-resistant population in Central Malaysia.**

J Glob Antimicrob Resist. 2022 Jun 15:S2213-7165(22)00143-6. doi: 10.1016/j.jgar.2022.06.009. Online ahead of print.

Zamri HF(1), Ruzan IN(2), Ramli SR(3), Ahmad N(3).

OBJECTIVES: Previous diversity studies on local Mycobacterium tuberculosis (MTB) isolates with or without antibiotic resistance, showed predominance of Indo-Oceanic EAI strains. This study focused specifically on a drug-resistant MTB population from central Malaysia and aimed to investigate the genotypes and resistance patterns involved.
METHODS: Whole-genome sequencing was performed on 56 local MTB isolates with known rifampicin-resistance or multidrug-resistance towards 13 anti-TB agents. Analysis of each genome sequence was performed using the widely recognized online MTB genotyping platforms, TBProfiler and Mykrobe to determine lineage and genotypic drug-resistance profile.
RESULTS: Forty (71.4%) isolates were identified as East-Asian Beijing strains. Phenotypic to genotypic antibiotic resistance patterns differed in 33 isolates (58.9%), with one isolate showing extensive drug resistance (XDR) that was previously not detected by conventional drug-susceptibility testing.
CONCLUSIONS: This drug-resistance population study demonstrated predominance of the East-Asian Beijing strains and a newly detected extensively drug-resistant MTB (XDR-TB) isolate in Malaysia. Information regarding association between lineage and drug-resistance TB in Malaysia is scarce, and more studies are needed to determine significance of such association, if any, in our local settings.

DOI: 10.1016/j.jgar.2022.06.009
PMID: 35717019

45. **The dynamic impacts of environmental-health and MDR-TB diseases and their influence on environmental sustainability at Chinese hospitals.**

Environ Sci Pollut Res Int. 2022 Jun;29(27):40531-40541. doi: 10.1007/s11356-022-19593-1. Epub 2022 Mar 30.

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

Erratum in
Environ Sci Pollut Res Int. 2022 Apr 23;:

The purpose of this study is to identify at what extent multidrug-resistant tuberculosis (MDR-TB) diseases effect on environmental health issues in selected provinces of Chinese hospitals. In survival analysis approach, this study employs the Cox proportional hazard model (CPM) to incorporate the duration of event, probability of occurrence of an event, and the issue of right censoring. An advantage of using CPM is that one does not need to specify the distribution of baseline hazard H0 (t) as it considers a common value for all units in population. The results indicate that male and travel expenditures have negative association with the duration of cure. Furthermore, the medical expenditures and the spatial characteristic of time expenditure have positive association with the duration of cure of MDR-TB patients. The inconsistent behavior of males in taking medicines as compared to females and males is also more prone to tuberculosis (TB).

DOI: 10.1007/s11356-022-19593-1
PMID: 35353303 [Indexed for MEDLINE]

46. **Bedaquiline Adherence Measured by Electronic Dose Monitoring Predicts Clinical Outcomes in the Treatment of Patients With Multidrug-Resistant Tuberculosis and HIV/AIDS.**

J Acquir Immune Defic Syndr. 2022 Jul 1;90(3):325-332. doi: 10.1097/QAI.0000000000002940.

O'Donnell MR(1)(2)(3), Padayatchi N(3), Wolf A(1)(2), Zelnick J(4), Daftary A(3)(5), Orrell C(6), Nimmo C(7)(8)(9), Baldwin M(1), Boodhram R(3), Maharaj B(3), Amico KR(10), Naidoo K(3), Friedland G(11).

BACKGROUND: Novel regimens have revolutionized multidrug-resistant tuberculosis (MDR-TB) treatment; however, medication adherence remains challenging and poorly characterized. We hypothesized that bedaquiline adherence, measured using electronic dose monitoring, would predict MDR-TB treatment outcomes.
SETTING: This is a prospective cohort study conducted in KwaZulu-Natal, South Africa.
METHODS: Adults with MDR-TB and HIV initiating bedaquiline and on antiretroviral

therapy (ART) were eligible. Separate electronic dose monitoring devices measured bedaquiline and ART adherence through 6 months, calculated as observed versus expected doses. Whole-genome sequencing was performed to identify bedaquiline resistance-associated variants.
RESULTS: From November 2016 through February 2018, 199 participants with MDR-TB and HIV were enrolled and followed up through treatment completion (median 17.2 months interquartile range 12.2-19.6). The median bedaquiline adherence was higher than ART adherence (97 vs. 89%, P < 0.001) but correlated (r2 = 0.68, P < 0.001). High bedaquiline adherence (≥90%) compared with lower adherence was associated with improved end of treatment successful outcome (83.4% vs. 46.3%, P < 0.001), decreased mortality (11.0% vs. 29.6% P = 0.004), and improved retention in care through end of treatment (94.5% vs. 79.6% P = 0.002). Modeling identified a highly significant but linear association between bedaquiline adherence and outcome. On multivariable analysis, bedaquiline adherence was independently associated with mortality and outcome. Bedaquiline resistance-associated variants were seen in 12% (7/57) of sequenced isolates (7% baseline, 5% emergent) with only 28.6% experiencing successful treatment outcome.
CONCLUSIONS: Bedaquiline adherence through 6 months independently predicted end of MDR-TB treatment outcome, but a specific bedaquiline adherence threshold was not identified. Interventions to optimize bedaquiline adherence are urgently needed to improve MDR-TB HIV treatment outcomes.

DOI: 10.1097/QAI.0000000000002940
PMID: 35195572 [Indexed for MEDLINE]

Conflict of interest statement: The authors have no conflicts of interest to disclose.

47. **Medical Care for Tuberculosis-HIV-Coinfected Patients in Russia with Respect to a Changeable Patients' Structure.**

Trop Med Infect Dis. 2022 May 31;7(6):86. doi: 10.3390/tropicalmed7060086.

Frolova OP(1)(2), Butylchenko OV(1), Gadzhieva PG(1), Timofeeva MY(3), Basangova VA(1), Petrova VO(4), Fadeeva IA(5), Kashutina MI(6)(7), Zabroda NN(4), Basov AA(4), Belova EV(4), Zhernov YV(4)(8), Mitrokhin OV(4), Enilenis II(1), Severova LP(1).

To date, tuberculosis (TB) remains the primary cause of mortality in human immunodeficiency virus (HIV) patients in Russia. Since the beginning of 2000, a sharp change in the HIV patients' structure, to the main known risk factors for

HIV infection has taken place in Russia. The transmission of HIV through injectable drug use has begun to decline significantly, giving way to the prevalence of sexual HIV transmission today. These changes may require adjustments to organizational approaches to anti-TB care and the treatment of HIV-positive patients. Our study is aimed at identifying changes in TB-HIV coinfection patients' structures in 2019 compared to 2000. Based on the results obtained, our goal was to point out the parameters that need to be taken into account when developing approaches to improve the organization of TB control care for people with HIV infection. We have carried out a cross-sectional, retrospective, epidemiological study using government TB registry data from four regions in two federal districts of Russia in 2019. The case histories of 2265 patients from two regions with high HIV prevalence, which are part of the Siberian Federal District of Russia, and 89 patient histories from two regions of low HIV prevalence, which are part of the Central Federal District of Russia, were analyzed. We found that parenteral transmission (69.4%) remains the primary route of HIV transmission among the TB-HIV coinfected. The unemployed of working age without disability account for 80.2% of all coinfected people, while the formerly incarcerated account for 53.7% and the homeless account for 4.1%. Those with primary multidrug-resistant TB (MDR-TB) comprise 56.2% of HIV-TB patients. When comparing the incidence of coinfection with HIV among TB patients, statistically significant differences were obtained. Thus, the chances of coinfection increased by 4.33 times among people with active TB (95% CI: 2.31; 8.12), by 2.97 times among people with MDR-TB (95% CI: 1.66; 5.32), by 5.2 times in people with advanced processes in the lungs, including destruction, (95% CI: 2.78; 9.7), as well as by 10.3 times in the case of death within the first year after the TB diagnosis (95% CI: 2.99; 35.5). The absence of data for the presence of TB during preventive examination was accompanied by a decrease in the chances of detecting coinfection (OR 0.36; 95% CI: 0.2; 0.64). We have identified the probable causes of the high incidence of TB among HIV-infected: HIV-patient social maladaptation usually results in delayed medical care, leading to TB treatment regimen violations. Furthermore, self-administration of drugs triggers MDR-TB within this group. Healthcare providers should clearly explain to patients the critical importance of immediately seeking medical care when initial TB symptoms appear.

DOI: 10.3390/tropicalmed7060086
PMCID: PMC9228798
PMID: 35736965

Conflict of interest statement: The authors declare that they have no conflicts of interest.

48. **Treatment outcomes 24 months after initiating short, all-oral bedaquiline-containing or injectable-containing rifampicin-resistant**

June 27th, 2022

tuberculosis treatment regimens in South Africa: a retrospective cohort study.

Lancet Infect Dis. 2022 Jul;22(7):1042-1051. doi: 10.1016/S1473-3099(21)00811-2. Epub 2022 May 2.

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

BACKGROUND: There is a need for short and safe all-oral treatment of rifampicin-resistant tuberculosis. We compared outcomes up to 24 months after treatment initiation for patients with rifampicin-resistant tuberculosis in South Africa treated with a short, all-oral bedaquiline-containing regimen (bedaquiline group), or a short, injectable-containing regimen (injectable group).
METHODS: Patients with rifampicin-resistant tuberculosis, aged 18 years or older, eligible for a short regimen starting treatment between Jan 1 and Dec 31, 2017, with a bedaquiline-containing or WHO recommended injectable-containing treatment regimen of 9-12 months, registered in the drug-resistant tuberculosis database (EDRWeb), and with known age, sex, HIV status, and national identification number were eligible for study inclusion; patients receiving linezolid, carbapenems, terizidone or cycloserine, delamanid, or para-aminosalicylic acid were excluded. Bedaquiline was given at a dose of 400 mg once daily for two weeks followed by 200 mg three times a week for 22 weeks. To compare regimens, patients were exactly matched on HIV and ART status, previous tuberculosis treatment history, and baseline acid-fast bacilli smear and culture result, while propensity score matched on age, sex, province of treatment, and isoniazid-susceptibility status. We did binomial linear regression to estimate adjusted risk differences (aRD) and 95% CIs for 24-month outcomes, which included: treatment success (ie, cure or treatment completion without evidence of recurrence) versus all other outcomes, survival versus death, disease free survival versus survival with treatment failure or recurrence, and loss to follow-up versus all other outcomes.
FINDINGS: Overall, 1387 (14%) of 10152 patients with rifampicin-resistant tuberculosis treated during 2017 met inclusion criteria; 688 in the bedaquiline group and 699 in the injectable group. Four patients (1%) had treatment failure or recurrence, 44 (6%) were lost to follow-up, and 162 (24%) died in the bedaquiline group, compared with 17 (2%), 87 (12%), and 199 (28%), respectively, in the injectable group. In adjusted analyses, treatment success was 14% (95% CI 8-20) higher in the bedaquiline group than in the injectable group (70% vs 57%); loss to follow-up was 4% (1-8) lower in the bedaquiline group (6% vs 12%); and disease-free survival was 2% (0-5) higher in the bedaquiline group (99% vs 97%). The bedaquiline group had 8% (4-11) lower risk of mortality during treatment (17·0% vs 22·4%), but there was no difference in mortality post-treatment.

INTERPRETATION: Patients in the bedaquiline group experienced significantly higher rates of treatment success at 24 months. This finding supports the use of short bedaquiline-containing regimens in eligible patients.
FUNDING: WHO Global TB Programme.
TRANSLATION: For the French translation of the abstract see Supplementary Materials section.

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

Conflict of interest statement: Declaration of interests We declare no competing interests.

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

J Infect. 2022 Jul;85(1):49-56. doi: 10.1016/j.jinf.2022.05.012. Epub 2022 May 16.

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

OBJECTIVES: Environmental and host-related factors that contribute to the transmission of multidrug-resistant tuberculosis (MDR-TB) have become an increasing concern, but the impact of bacterial genetic factors associated with bacterial fitness on MDR-TB transmission is poorly understood. Here, we present a global view of the correlation between common fitness-related genotypes and MDR-TB transmission by analyzing a representative number of MDR-TB isolates.
METHODS: We assembled a global whole genome sequencing (WGS) dataset of MDR-TB strains collected through retrospective cohorts or population-based approaches using public databases and literature curation. WGS-based clusters were defined as groups of strains with genomic difference of ≤ 5 SNPs.
RESULTS: We curated high-quality WGS data of 4696 MDR-TB isolates from 17 countries with a mean clustering rate of 48% (range 0-100%). Correlational analysis showed that increased risk of MDR-TB strain clustering was not associated with compensatory mutations (OR 1.07, 95% CI 0.72-1.59), low-fitness cost drug-resistant mutations (katG S315T: OR 1.42, 95% CI 0.82-2.47; rpoB

S450L: OR 1.26, 95% CI 0.87-1.83) or Lineage 2 (OR 1.50, 95% CI 0.95-2.39).
CONCLUSIONS: The factors most commonly thought to increase bacterial fitness were not significantly associated with increased MDR-TB transmission, and thus do not appear to be major contributors to the current epidemic of MDR-TB.

DOI: 10.1016/j.jinf.2022.05.012
PMID: 35588941 [Indexed for MEDLINE]

Conflict of interest statement: Declaration of Competing Interest None declared.

50. **The global impact of household contact management for children on multidrug-resistant and rifampicin-resistant tuberculosis cases, deaths, and health-system costs in 2019: a modelling study.**

Lancet Glob Health. 2022 Jul;10(7):e1034-e1044. doi: 10.1016/S2214-109X(22)00113-9. Epub 2022 May 18.

Dodd PJ(1), Mafirakureva N(2), Seddon JA(3), McQuaid CF(4).

BACKGROUND: Estimates suggest that at least 30 000 children develop multidrug-resistant or rifampicin-resistant tuberculosis each year. Despite household contact management (HCM) being widely recommended, it is rarely done.
METHODS: We used mathematical modelling to evaluate the potential country-level and global effects and cost-effectiveness of multidrug-resistant or rifampicin-resistant tuberculosis HCM for children younger than 15 years who are living with a person with newly diagnosed multidrug-resistant or rifampicin-resistant tuberculosis. We compared a baseline of no HCM with several HCM strategies and tuberculosis preventive therapy regimens, calculating the effect on multidrug-resistant or rifampicin-resistant tuberculosis cases, deaths, and health-system costs. All HCM strategies involved the screening of children for prevalent tuberculosis disease but with tuberculosis preventive therapy either not given or targeted dependent on age, HIV status, and result of tuberculin skin test. We evaluated the use of fluoroquinolones (ie, levofloxacin and moxifloxacin), delamanid, and bedaquiline as tuberculosis preventive therapy.
FINDINGS: Compared with a baseline without HCM, HCM for all adults diagnosed with multidrug-resistant or rifampicin-resistant tuberculosis in 2019 would have entailed screening 227 000 children (95% uncertainty interval [UI]: 205 000-252 000) younger than 15 years globally, and averted 2350 tuberculosis deaths (1940-2790), costing an additional US$63 million (74-95 million). If all the children within the household who had been in contact with the person with multidrug-resistant or rifampicin-resistant tuberculosis received tuberculosis

preventive therapy with levofloxacin, 5620 incident tuberculosis cases (95% UI 4540-6890) and an additional 1240 deaths (970-1540) would have been prevented. Incremental cost-effectiveness ratios were lower than half of per-capita gross domestic product for most interventions in most countries. Targeting only children younger than 5 years and those living with HIV reduced the number of incident cases and deaths averted, but improved cost-effectiveness. Tuberculosis preventive therapy with delamanid increased the effect, in terms of reduced incidence and mortality, compared with levofloxacin.
INTERPRETATION: HCM for patients with multidrug-resistant or rifampicin-resistant tuberculosis is cost-effective in most settings and could avert a substantial proportion of multidrug-resistant or rifampicin-resistant tuberculosis cases and deaths in children globally.
FUNDING: UK Medical Research Council.

DOI: 10.1016/S2214-109X(22)00113-9
PMCID: PMC9197775
PMID: 35597248 [Indexed for MEDLINE]

Conflict of interest statement: Declaration of interests We declare no competing interests.

51. **CRISPRi chemical genetics and comparative genomics identify genes mediating drug potency in Mycobacterium tuberculosis.**

Nat Microbiol. 2022 Jun;7(6):766-779. doi: 10.1038/s41564-022-01130-y. Epub 2022 May 30.

Li S(#)(1), Poulton NC(#)(1), Chang JS(1), Azadian ZA(1), DeJesus MA(1), Ruecker N(2), Zimmerman MD(3), Eckartt KA(1), Bosch B(1), Engelhart CA(2), Sullivan DF(2), Gengenbacher M(3)(4), Dartois VA(3)(4), Schnappinger D(2), Rock JM(5).

Mycobacterium tuberculosis (Mtb) infection is notoriously difficult to treat. Treatment efficacy is limited by Mtb's intrinsic drug resistance, as well as its ability to evolve acquired resistance to all antituberculars in clinical use. A deeper understanding of the bacterial pathways that influence drug efficacy could facilitate the development of more effective therapies, identify new mechanisms of acquired resistance, and reveal overlooked therapeutic opportunities. Here we developed a CRISPR interference chemical-genetics platform to titrate the expression of Mtb genes and quantify bacterial fitness

in the presence of different drugs. We discovered diverse mechanisms of intrinsic drug resistance, unveiling hundreds of potential targets for synergistic drug combinations. Combining chemical genetics with comparative genomics of Mtb clinical isolates, we further identified several previously unknown mechanisms of acquired drug resistance, one of which is associated with a multidrug-resistant tuberculosis outbreak in South America. Lastly, we found that the intrinsic resistance factor whiB7 was inactivated in an entire Mtb sublineage endemic to Southeast Asia, presenting an opportunity to potentially repurpose the macrolide antibiotic clarithromycin to treat tuberculosis. This chemical-genetic map provides a rich resource to understand drug efficacy in Mtb and guide future tuberculosis drug development and treatment.

DOI: 10.1038/s41564-022-01130-y
PMCID: PMC9159947
PMID: 35637331 [Indexed for MEDLINE]

Conflict of interest statement: All authors declare no competing interests.

52. **Uncovering the Mast Cell Response to Mycobacterium tuberculosis.**

Front Immunol. 2022 Jun 2;13:886044. doi: 10.3389/fimmu.2022.886044. eCollection 2022.

Torres-Atencio I(1)(2), Campble A(2), Goodridge A(2), Martin M(3)(4).

The immunologic mechanisms that contribute to the response to Mycobacterium tuberculosis infection still represent a challenge in the clinical management and scientific understanding of tuberculosis disease. In this scenario, the role of the different cells involved in the host response, either in terms of innate or adaptive immunity, remains key for defeating this disease. Among this coordinated cell response, mast cells remain key for defeating tuberculosis infection and disease. Together with its effector's molecules, membrane receptors as well as its anatomical locations, mast cells play a crucial role in the establishment and perpetuation of the inflammatory response that leads to the generation of the granuloma during tuberculosis. This review highlights the current evidences that support the notion of mast cells as key link to reinforce the advancements in tuberculosis diagnosis, disease progression, and novel therapeutic strategies. Special focus on mast cells capacity for the modulation of the inflammatory response among patients suffering multidrug resistant tuberculosis or in co-infections such as current COVID-19 pandemic.

DOI: 10.3389/fimmu.2022.886044
PMCID: PMC9201906
PMID: 35720353 [Indexed for MEDLINE]

Conflict of interest statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. The reviewer RMC declared a past co-authorship with the author MM to the handling editor.

53. **Novel 2-arylthiazolidin-4-one-thiazole hybrids with potent activity against Mycobacterium tuberculosis.**

Bioorg Chem. 2022 Jul;124:105809. doi: 10.1016/j.bioorg.2022.105809. Epub 2022 Apr 14.

Othman DIA(1), Hamdi A(1), Abdel-Aziz MM(2), Elfeky SM(3).

Substituted aldehydes, ethyl 2-(2-amino-thiazol-4-yl)acetate), and 2-mercaptoacetic acid, in a three-component one-pot green synthetic approach afforded 2-arylthiazolidin-4-one- thiazole hybrids(T1-T13). Compounds showed good anti-tubercular activity towards sensitive M. tuberculosis strain. Compound T8 was as potent as isoniazide (INH) with MIC = 0.12 μg/ml. Compounds T2 and T13 showed potent activity with MIC = 0.48 μg/ml. Other compounds showed moderate to good anti-tubercular activity towards MDR M. tuberculosis strain with MIC range 1.95-125 μg/ml. Compounds T2, T8, T9, and T13 showed anti-tubercular activity towards XDR M. tuberculosis strain with MIC range 7.81-125 μg/ml. Compounds T2 and T8 were capable of inhibiting M. tuberculosis InhA enzyme in-vitro with IC50 = 1.3 ± 0.61 μM and 1.06 ± 0.97 μM, respectively. Molecular docking simulation showed that T2 and T8 were also capable of interacting at the catalytic site of InhA enzyme in a similar mode to the native ligand through binding with NAD+ and Tyr158. The 3D- QSAR study highlighted the relevance of substitution of phenyl group at position-2 of thiazolidin-4-one where bulky electronegative substitution at position-4 of the phenyl ring favored the activity against M. tuberculosis H37R. Additionally, compounds showed good antibacterial activity against bronchitis causing bacteria M. pneumoniae, S. pneumonia, K. pneumonia, and B. pertussis compared to Azithromycin. In-silico studies of ADMET descriptors and drug-likeness were conducted for all synthesized compounds. Compounds showed good oral bioavailability, good gastrointestinal absorption and showed no signs of adverse effects to the liver or CNS. Compounds showed no potential carcinogenicity as well.

DOI: 10.1016/j.bioorg.2022.105809
PMID: 35447406 [Indexed for MEDLINE]

54. **Mesoporous silica nanocarriers as drug delivery systems for anti-tubercular agents: a review.**

R Soc Open Sci. 2022 Jun 8;9(6):220013. doi: 10.1098/rsos.220013. eCollection 2022 Jun.

Tella JO(1), Adekoya JA(1), Ajanaku KO(1).

The treatment and management of tuberculosis using conventional drug delivery systems remain challenging due to the setbacks involved. The lengthy and costly treatment regime and patients' non-compliance have led to drug-resistant tuberculosis, which is more difficult to treat. Also, anti-tubercular drugs currently used are poor water-soluble drugs with low bioavailability and poor therapeutic efficiency except at higher doses which causes drug-related toxicity. Novel drug delivery carrier systems such as mesoporous silica nanoparticles (MSNs) have been identified as nanomedicines capable of addressing the challenges mentioned due to their biocompatibility. The review discusses the sol-gel synthesis and chemistry of MSNs as porous drug nanocarriers, surface functionalization techniques and the influence of their physico-chemical properties on drug solubility, loading and release kinetics. It outlines the physico-chemical characteristics of MSNs encapsulated with anti-tubercular drugs.

DOI: 10.1098/rsos.220013
PMCID: PMC9174711
PMID: 35706676

55. **Determination of genetic diversity of multidrug-resistant Mycobacterium tuberculosis strains in Turkey using 15 locus MIRU-VNTR and spoligotyping methods.**

Pathog Glob Health. 2022 Jun 1:1-7. doi: 10.1080/20477724.2022.2084807. Online ahead of print.

Gürer Giray B(1), Aslantürk A(2), Şimşek H(3), Özgür D(4), Kılıç S(5), Aslan G(6).

Tuberculosis (TB) remains the leading cause of deaths from infectious disease

worldwide. Nowadays, the tendency of Mycobacterium tuberculosis complex (MTBC) to spread between continents due to uncontrolled migration movements shows that TB is a global health problem. The number of studies for the detection of MTBC strains' epidemiological features in areas with TB spread risk using molecular-based methods such as spoligotyping and Mycobacterial Interspersed Repetitive Unit (MIRU) Variable Number Tandem Repeats (VNTR) at the clonal level is insufficient. In this study, it was aimed to determine the phylogenetic relationships of MTBC strains at the species level by spoligotyping and 15 locus MIRU-VNTR (MIRU-VNTR15) molecular methods of 96 multidrug-resistant (MDR) MTBC strains isolated from sputum samples of patients with a preliminary diagnosis of pulmonary TB or suspected contact history those sent to National Tuberculosis Reference Laboratory from the centers that are members of the Tuberculosis Laboratory Surveillance Network. The phylogenetic relationship between 96 MDR-TB strains was investigated with the combination of bead-based spoligotyping and MIRU-VNTR15 methods on the MAGPIX® Milliplex Map device. In this study, it was determined that the T1 family is more common in our country and LAM7-TUR family is less common than the Beijing family unlike other studies. It was determined that the strains in the same cluster had different locus profiles, and there was no transmission from the same clone in the clonal typing we performed with spoligotyping and MIRU-VNTR15.

DOI: 10.1080/20477724.2022.2084807
PMID: 35642888

56. **Pharmacokinetics and Dose Optimization Strategies of Para-Aminosalicylic Acid in Children with Rifampicin-Resistant Tuberculosis.**

Antimicrob Agents Chemother. 2022 Jun 21;66(6):e0226421. doi: 10.1128/aac.02264-21. Epub 2022 May 4.

van der Laan LE(1)(2), Garcia-Prats AJ(2), Schaaf HS(2), Chirehwa M(1), Winckler JL(2), Mao J(2), Draper HR(2), Wiesner L(1), Norman J(1), McIlleron H(1), Donald PR(2), Hesseling AC(#)(2), Denti P(#)(1).

Treatment options for children with Rifampicin-resistant tuberculosis (RR-TB) remain limited, and para-aminosalicylic acid (PAS) is still a relevant component of treatment regimens. Prevention of resistance to companion drugs by PAS is dose related, and at higher concentrations, PAS may exhibit significant bactericidal activity in addition to its bacteriostatic properties. The optimal dosing of PAS in children is uncertain, specifically for delayed-release granule preparations, which are the most used. A population pharmacokinetic model was developed describing PAS pharmacokinetics in children receiving routine RR-TB treatment. Model-based simulations evaluated current World Health Organization (WHO) weight-band doses against the adult pharmacokinetic target of 50 to 100

mg/liter for peak concentrations. Of 27 children included, the median (range) age and weight were 3.87 (0.58 to 13.7) years and 13.3 (7.15 to 30.5) kg, respectively; 4 (14.8%) were HIV positive. PAS followed one-compartment kinetics with first-order elimination and transit compartment absorption. The typical clearance in a 13-kg child was 9.79 liters/h. Increased PAS clearance was observed in both pharmacokinetic profiles from the only patient receiving efavirenz. No effect of renal function, sex, ethnicity, nutritional status, HIV status, antiretrovirals (lamivudine, abacavir, and lopinavir-ritonavir), or RR-TB drugs was detected. In simulations, target concentrations were achieved only using the higher WHO dose range of 300 mg/kg once daily. A transit compartment adequately describes absorption for the slow-release PAS formulation. Children should be dosed at the higher range of current WHO-recommended PAS doses and in a once-daily dose to optimize treatment.

DOI: 10.1128/aac.02264-21
PMCID: PMC9211416
PMID: 35506699 [Indexed for MEDLINE]

Conflict of interest statement: The authors declare no conflict of interest.

57. **Prediction of drug resistance profile of multidrug-resistant Mycobacterium tuberculosis (MDR-MTB) isolates from newly diagnosed case by whole genome sequencing (WGS): a study from a high tuberculosis burden country.**

BMC Infect Dis. 2022 May 27;22(1):499. doi: 10.1186/s12879-022-07482-4.

Sun W(#)(1), Gui X(#)(1), Wu Z(2), Zhang Y(3), Yan L(4).

OBJECTIVES: Our aim was to assess the ability of the Whole-genome sequencing (WGS) in predicting drug resistance profile of multidrug-resistant mycobacterium tuberculosis (MDR-MTB) from newly diagnosed cases in China.
METHODS: We validated the Phenotypic drug Sensitivity Test (pDST) for 12 anti-tuberculosis drugs using the Bactec MGIT 960 system. We described the characteristics of the isolates enrolled and compared the pDST results with resistance profiles predicted by WGS.
RESULTS: The pDST showed that of the 43 isolates enrolled, 25.6% were sensitive to rifabutin (RFB); 97.7%、97.7%、93.0% and 93.0% were sensitive to cycloserine (Cs), amikacin/kanamycin (Ak/Km), para-aminosalicylic acid (Pas) and ethionamide Eto), respectively; 18.6% were resistant to fluoroquinolones (FQs) or second-line injections. Genotype DST determined by WGS of Ak/Km、Eto and RFP reached high consistency to 97.7% compared with pDST, followed by moxifloxacin (Mfx) 95.3%, levofloxaci (Lfx) and Pas 93%, streptomycin (Sm) 90.3%. The genotype DST of RFB and EMB showed low consistency with the pDST of 67.2 and 79.1%. WGS also detected 27.9% isolates of pyrazinamide(PZA)-related

drug-resistant mutation. No mutations associated with linezolid (Lzd), bedaquiline (Bdq) and clofazimine (Cfz) were detectd.
CONCLUSIONS: WGS has the potential to infer resistance profiles without time-consuming phenotypic methods, which could be provide a basis to formulate reasonable treatment in high TB burden areas.

DOI: 10.1186/s12879-022-07482-4
PMCID: PMC9137048
PMID: 35624432 [Indexed for MEDLINE]

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

58. **Global availability of susceptibility testing for second-line anti-tuberculosis agents.**

Int J Tuberc Lung Dis. 2022 Jun 1;26(6):524-528. doi: 10.5588/ijtld.21.0420.

Lazarchik A(1), Nyaruhirira AU(2), Chiang CY(3), Wares F(4), Horsburgh CR(5).

BACKGROUND: The continued development of new anti-TB agents brings with it a demand for accompanying treatment regimens to prevent the development of resistance. Effectively meeting this demand requires an understanding of the pathogen´s susceptibility to various treatment options, which in turn makes access to antibiotic susceptibility testing (AST) a paramount consideration in the global treatment of TB.METHODS: A 12-question, quantitative and qualitative survey was developed to gauge global capacity and access to AST. The survey was disseminated to members of the Global Laboratory Initiative, Global Drug-resistant TB Initiative, and the TB section of the International Union Against Tuberculosis and Lung Disease to solicit responses from pertinent stakeholders.RESULTS: A total of 323 complete responses representing 84 countries and all WHO Regions were collected. AST capacity for fluoroquinolones and second-line injectables was high in all WHO Regions. AST capacity for the new and repurposed drugs is highest in the European Region, Region of the Americas and the Western Pacific Region, but quite limited in the African and Eastern Mediterranean Regions. The AST turnaround time for second-line drugs was delayed compared to that for first-line drugs as samples needed to be sent farther for analysis. Common barriers to AST for second-line drugs were lack of specimen transportation infrastructure, high costs, and lack of specialised laboratory workers and specialised laboratory facilities.CONCLUSION: Without expanding global access to AST, the growing availability of new treatment options will likely be threatened by accompanying increase in resistance. There

is an earnest and pressing need to improve capacity and access to AST alongside treatment options.

DOI: 10.5588/ijtld.21.0420
PMID: 35650708 [Indexed for MEDLINE]

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

Eur J Med Chem. 2022 Jul 5;237:114404. doi: 10.1016/j.ejmech.2022.114404. Epub 2022 Apr 21.

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

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

DOI: 10.1016/j.ejmech.2022.114404
PMID: 35486992 [Indexed for MEDLINE]

60. **Co-administration of treatment for rifampicin-resistant TB and chronic HCV infection: A TBnet and ESGMYC study.**

J Infect. 2022 Jun;84(6):834-872. doi: 10.1016/j.jinf.2022.03.004. Epub 2022 Mar 7.

Tunesi S(1), Dû DL(2), Gualano G(3), Millet JP(4), Skrahin A(5), Bothamley G(6), Casas X(7), Goletti D(3), Lange C(8), Musso M(3), Palmieri F(3), Pourcher V(9), Rioux C(10), Skrahina A(5), Veziris N(11), Viatushka D(5), Jachym-Fréchet M(2),

Guglielmetti L(12); TBnet, The ESGMYC, and The French MDR-TB Group.

Collaborators: Marigot-Outtandy D(13), Lescure X(14), Dubert M(14), Yazdanpanah Y(14), Caumes E(15), Choinier P(15), Haddad E(15), Kowalczyk J(16), Laurichesse H(17), Lesens O(17), Aubry A(18), Bonnet I(18), Morel F(18).

DOI: 10.1016/j.jinf.2022.03.004
PMID: 35271917 [Indexed for MEDLINE]

61. **A novel class of antimicrobial drugs selectively targets a Mycobacterium tuberculosis PE-PGRS protein.**

PLoS Biol. 2022 May 31;20(5):e3001648. doi: 10.1371/journal.pbio.3001648. eCollection 2022 May.

Seo H(1)(2), Kim S(1)(2), Mahmud HA(1), Islam MI(1), Yoon Y(1), Cho HD(3), Nam KW(4), Choi J(5), Gil YS(6), Lee BE(2), Song HY(1)(2).

The continued spread of drug-resistant tuberculosis is one of the most pressing and complex challenges facing tuberculosis management worldwide. Therefore, developing a new class of drugs is necessary and urgently needed to cope with the increasing threat of drug-resistant tuberculosis. This study aims to discover a potential new class of tuberculosis drug candidates different from existing tuberculosis drugs. By screening a library of compounds, methyl (S)-1-((3-alkoxy-6,7-dimethoxyphenanthren-9-yl)methyl)-5-oxopyrrolidine-2-carboxylate (PP) derivatives with antitubercular activity were discovered. MIC ranges for PP1S, PP2S, and PP3S against clinically isolated drug-resistant Mycobacterium tuberculosis strains were 0.78 to 3.13, 0.19 to 1.56, and 0.78 to 6.25 μg/ml, respectively. PPs demonstrated antitubercular activities in macrophage and tuberculosis mouse models, showing no detectable toxicity in all assays tested. PPs specifically inhibited M. tuberculosis without significantly changing the intestinal microbiome in mice. Mutants selected in vitro suggest that the drug targets the PE-PGRS57, which has been found only in the genomes of the M. tuberculosis complex, highlighting the specificity and safety potency of this compound. As PPs show an excellent safety profile and highly selective toxicity specific to M. tuberculosis, PPs are considered a promising new candidate for the treatment of drug-resistant tuberculosis while maintaining microbiome homeostasis.

DOI: 10.1371/journal.pbio.3001648
PMCID: PMC9154192
PMID: 35639773 [Indexed for MEDLINE]

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

62. **Population Pharmacokinetics of Delamanid and its Main Metabolite DM-6705 in Drug-Resistant Tuberculosis Patients Receiving Delamanid Alone or Coadministered with Bedaquiline.**

Clin Pharmacokinet. 2022 Jun 7. doi: 10.1007/s40262-022-01133-2. Online ahead of print.

Tanneau L(1), Karlsson MO(1), Diacon AH(2), Shenje J(3), De Los Rios J(4), Wiesner L(5), Upton CM(2), Dooley KE(6), Maartens G(5), Svensson EM(7)(8).

BACKGROUND AND OBJECTIVE: Delamanid is a nitroimidazole, a novel class of drug for treating tuberculosis, and is primarily metabolized by albumin into the metabolite DM-6705. The aims of this analysis were to develop a population pharmacokinetic (PK) model to characterize the concentration-time course of delamanid and DM-6705 in adults with drug-resistant tuberculosis and to explore a potential drug-drug interaction with bedaquiline when coadministered.
METHODS: Delamanid and DM-6705 concentrations after oral administration, from 52 participants (of whom 26 took bedaquiline concurrently and 20 were HIV-1 positive) enrolled in the DELIBERATE trial were analyzed using nonlinear mixed-effects modeling.
RESULTS: Delamanid PK were described by a one-compartment disposition model with transit compartment absorption (mean absorption time of 1.45 h [95% confidence interval 0.501-2.20]) and linear elimination, while the PK of DM-6705 metabolite were described by a one-compartment disposition model with delamanid clearance as input and linear elimination. Predicted terminal half-life values for delamanid and DM-6705 were 15.1 h and 7.8 days, respectively. The impact of plasma albumin concentrations on delamanid metabolism was not significant. Bedaquiline coadministration did not affect delamanid PK. Other than allometric scaling with body weight, no patients' demographics were significant (including HIV).
CONCLUSIONS: This is the first joint PK model of delamanid and its DM-6705 metabolite. As such, it can be utilized in future exposure-response or exposure-safety analyses. Importantly, albumin concentrations, bedaquiline coadministration, and HIV co-infection (dolutegravir coadministration) did not have an effect on delamanid and DM-6705 PK.

DOI: 10.1007/s40262-022-01133-2
PMID: 35668346

63. **Exploration of Isoxazole-Carboxylic Acid Methyl Ester Based 2-Substituted Quinoline Derivatives as Promising Antitubercular Agents.**

Chem Biodivers. 2022 Jun 2:e202200324. doi: 10.1002/cbdv.202200324. Online ahead of print.

Kumar Sahoo S(1), Naiyaz Ahmad M(2)(3), Kaul G(2)(3), Nanduri S(1), Dasgupta A(2)(3), Chopra S(2)(3), Madhavi Yaddanapudi V(1).

In pursuit of potent anti-TB agents active against drug resistant tuberculosis (DR-TB), herein we report synthesis and bio-evaluation of a new series of isoxazole-carboxylic acid methyl ester based 2-substituted quinoline derivatives. Preliminary evaluation indicated selectivity towards Mtb H37Rv, with no inhibition of non-tubercular mycobacterial (NTM) & bacterial pathogen panel. Out of 36 synthesized compounds, majority exhibited substantial inhibition of Mtb H37Rv (MIC 0.5-8 μg/mL). Cell viability test against Vero cells revealed no significant cytotoxicity. Further, screening against drug resistant strains (DR-Mtb) found hit compound displaying promising potency (MIC 1-4 μg/mL). Structure optimization of the hit led to the identification of lead compound demonstrating potent inhibition of both drug-susceptible Mtb (MIC 0.12 μg/mL) and drug-resistant Mtb (MIC 0.25-0.5 μg/mL) along with a high selectivity index (SI) >80. Taken together, with appreciable selectivity and potent activity, these chemotypes show prospect to be turned into a potential anti-TB candidate.

DOI: 10.1002/cbdv.202200324
PMID: 35653161

64. **Insights into innovative therapeutics for drug-resistant tuberculosis: Host-directed therapy and autophagy inducing modified nanoparticles.**

Int J Pharm. 2022 Jun 25;622:121893. doi: 10.1016/j.ijpharm.2022.121893. Epub 2022 Jun 6.

Khoza LJ(1), Kumar P(1), Dube A(2), Demana PH(3), Choonara YE(4).

DOI: 10.1016/j.ijpharm.2022.121893
PMCID: PMC9169426
PMID: 35680110 [Indexed for MEDLINE]

Conflict of interest statement: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

65. **Pharmacokinetics of bedaquiline in cerebrospinal fluid (CSF) in patients with pulmonary tuberculosis (TB).**

J Antimicrob Chemother. 2022 May 29;77(6):1720-1724. doi: 10.1093/jac/dkac067.

Upton CM(1), Steele CI(2), Maartens G(2), Diacon AH(1), Wiesner L(2), Dooley KE(3).

BACKGROUND: With current treatment options most patients with CNS TB develop severe disability or die. Drug-resistant tuberculous meningitis is nearly uniformly fatal. Novel treatment strategies are needed. Bedaquiline, a potent anti-TB drug, has been reported to be absent from CSF in a single report.
OBJECTIVES: To explore the pharmacokinetics of bedaquiline and its M2 metabolite in the CSF of patients with pulmonary TB.
PATIENTS AND METHODS: Individuals with rifampicin-resistant pulmonary TB established on a 24 week course of treatment with bedaquiline underwent a lumbar puncture along with multiple blood sample collections over 24 h for CSF and plasma pharmacokinetic assessment, respectively. To capture the expected low bedaquiline and M2 concentrations (due to high protein binding in plasma) we optimized CSF collection and storage methods in vitro before concentrations were quantified via liquid chromatography with tandem MS.
RESULTS: Seven male participants were enrolled, two with HIV coinfection. Using LoBind® tubes lined with a 5% BSA solution, bedaquiline and M2 could be accurately measured in CSF. Bedaquiline and M2 were present in all patients at all timepoints at concentrations similar to the estimated unbound fractions in plasma.
CONCLUSIONS: Bedaquiline and M2 penetrate freely into the CSF of pulmonary TB patients with a presumably intact blood-brain barrier. Clinical studies are urgently needed to determine whether bedaquiline can contribute meaningfully to the treatment of CNS TB.

DOI: 10.1093/jac/dkac067
PMID: 35257182 [Indexed for MEDLINE]

66. **Moxifloxacin concentration correlate with QTc interval in rifampicin-resistant**

tuberculosis patients on shorter treatment regimens.

J Clin Tuberc Other Mycobact Dis. 2022 Jun 6;28:100320. doi: 10.1016/j.jctube.2022.100320. eCollection 2022 Aug.

Kusmiati T(1)(2)(3), Made Mertaniasih N(4)(3), Nugroho Eko Putranto J(5), Suprapti B(6), Luthfah N(5), Soedarsono S(2)(3), Koesoemoprodjo W(2), Prawita Sari A(2).

BACKGROUND: Drug-resistant tuberculosis (DR-TB) continues to be a global threat. Moxifloxacin is one of the components of the shorter treatment regimen which is suspected to increase the risk of QT prolongation, although it is also likely to be the most effective against DR-TB. A study to evaluate the correlation between the concentration of moxifloxacin and QTc interval in RR-TB patients who received shorter regimens is needed.
METHODS: This was an observational study in 2 groups of RR-TB patients on shorter treatment regimens (intensive phase and continuation phase), contain moxifloxacin with body weight-adjusted dose. Blood samples were collected at 2 h after taking the 48th-hour dose and 1 h before taking the 72nd-hour dose.
RESULTS: Forty-five RR-TB patients were included in this study. At 2 h after taking the 48th-hour dose, the mean of QTc interval in intensive phase and continuation phase was 444.38 ms vs. 467.94 ms, p = 0.026, while mean of moxifloxacin concentration in intensive phase and continuation phase was 4.3 μg/mL vs. 4.61 μg/mL, p = 0.686). At 1 h before taking the 72nd-hour dose, both moxifloxacin concentration and QTc interval in intensive phase and continuation showed no significant difference with p-value of 0.610 and 0.325, respectively. At 2 h after taking the 48th-dose, moxifloxacin concentration did not correlate with QTc interval, both in intensive phase (p = 0.576) and in continuation phase (p = 0.691). At 1 h before taking the 72nd-hour dose, moxifloxacin concentration also did not correlate with QTc interval in intensive phase (p = 0.531) and continuation phase (p = 0.209).
CONCLUSIONS: Our study found that moxifloxacin concentration did not correlate with QTc interval, which indicates the safe use of moxifloxacin on QTc interval. In addition to close monitoring of QTc interval, the clinicians should also consider other variables which potentially increase risk for QTc prolongation in DR-TB patients who received shorter treatment regimens.

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PMCID: PMC9189108
PMID: 35706565

Conflict of interest statement: The authors declare that they have no known

competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

67. **Harnessing new mHealth technologies to Strengthen the Management of Multidrug-Resistant Tuberculosis in Vietnam (V-SMART trial): a protocol for a randomised controlled trial.**

BMJ Open. 2022 Jun 22;12(6):e052633. doi: 10.1136/bmjopen-2021-052633.

Velen K(1), Nguyen VN(2), Nguyen BH(2), Dang T(3), Nguyen HA(4), Vu DH(4), Do TT(2), Pham Duc C(3), Nguyen HL(5), Pham HT(6), Marais BJ(7), Johnston J(8), Britton W(9)(10), Beardsley J(7), Negin J(11), Wiseman V(12)(13), Marks GB(14), Nguyen TA(15), Fox GJ(3)(16).

INTRODUCTION: Multidrug-resistant tuberculosis (MDR-TB) remains a major public health problem globally. Long, complex treatment regimens coupled with frequent adverse events have resulted in poor treatment adherence and patient outcomes. Smartphone-based mobile health (mHealth) technologies offer national TB programmes an appealing platform to improve patient care and management; however, clinical trial evidence to support their use is lacking. This trial will test the hypothesis that an mHealth intervention can improve treatment success among patients with MDR-TB and is cost-effective compared with standard practice.
METHODS AND ANALYSIS: A community-based, open-label, parallel-group randomised controlled trial will be conducted among patients treated for MDR-TB in seven provinces of Vietnam. Patients commencing therapy for microbiologically confirmed rifampicin-resistant or multidrug-resistant tuberculosis within the past 30 days will be recruited to the study. Participants will be individually randomised to an intervention arm, comprising use of an mHealth application for treatment support, or a 'standard care' arm. In both arms, patients will be managed by the national TB programme according to current national treatment guidelines. The primary outcome measure of effectiveness will be the proportion of patients with treatment success (defined as treatment completion and/or bacteriological cure) after 24 months. A marginal Poisson regression model estimated via a generalised estimating equation will be used to test the effect of the intervention on treatment success. A prospective microcosting of the intervention and within-trial cost-effectiveness analysis will also be undertaken from a societal perspective. Cost-effectiveness will be presented as an incremental cost per patient successfully treated and an incremental cost per quality-adjusted life-year gained.
ETHICS: Ethical approval for the study was granted by The University of Sydney Human Research Ethics Committee (2019/676).
DISSEMINATION: Study findings will be disseminated to participants and published

in peer-reviewed journals and conference proceedings.
TRIAL REGISTRATION NUMBER: ACTRN12620000681954.

DOI: 10.1136/bmjopen-2021-052633
PMID: 35732397 [Indexed for MEDLINE]

Conflict of interest statement: Competing interests: None declared.

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

Expert Rev Anti Infect Ther. 2022 Jun;20(6):955-961. doi: 10.1080/14787210.2022.2016392. Epub 2022 Jan 2.

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

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

DOI: 10.1080/14787210.2022.2016392
PMID: 34913825 [Indexed for MEDLINE]

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

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

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

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

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

70. **Novel rrs mutations in second-line injectable drug-resistant clinical isolates of Mycobacterium tuberculosis from the Punjab province of Pakistan.**

J Infect Chemother. 2022 Aug;28(8):1119-1124. doi: 10.1016/j.jiac.2022.03.027. Epub 2022 Apr 12.

Sarwer MI(1), Khan MT(2), Khurshid S(3).

INTRODUCTION: Phenotypic drug susceptibility testing is the most common approach to assess drug-resistant isolates; however, molecular methods of drug susceptibility testing are fast, accurate hence, offer less time for transmission during the diagnosis period. As data on the molecular methods regarding injectable drug resistance in the Punjab province of Pakistan is limited, therefore in this study, we aimed to analyze the mutations in the rrs gene behind second-line injectable drug resistance.
MATERIAL AND METHODS: Mycobacterium tuberculosis isolates were collected from the sputum of 5362 TB suspects. The strains confirmed for resistant to injectable drugs through drug susceptibility testing were further proceeded. The 1537bp rrs gene was amplified with the help of three sets of primers with overlapping regions and DNA sequencing was performed. Obtained sequences were aligned with reference sequence to find mutations. RFLP-PCR method was also optimized for rapid detection of a common (143bp and 205bp) rrs gene mutation.
RESULTS: Among 172 rifampicin resistance isolates, 163(95%) were resistant to both rifampicin and isoniazid, and 9 (5%) were resistant to only rifampicin. Among the resistant samples, 12 (6.9%) samples were resistant to all three injectable drugs. Sixty out of 172 (34.9%) samples showed resistance to at least one drug and 10 (5.8%) samples were resistant to two drugs among the 3 s-line drugs. Sequencing analysis showed novel mutations in different samples at positions 443InsC, 19DelT, 29G>A, 48C>T, 50G>C, 265InsT, 423T>G, 476InsA, 446A>G, 563DelA, 695G>A, 805DelA, 900G>A, and 1510A>G, while some already reported mutations at position 1401A>G, 1402A>G, and 1484G>T were also observed. MIC of novel rrs gene mutations in KAN, CAP, and AMK resistant isolates were found between 2.5 mg/L-3.05 mg/L, 2.08 mg/L-3.0 mg/L, and 2.1 mg/L-2.7 mg/L respectively.
CONCLUSION: Novel mutations in the rrs gene reported in this study may confer second-line injectable drugs resistance in Mtb. This molecular insight into second-line injectable drug resistance is useful for better management of resistance Mtb in high burden countries.

DOI: 10.1016/j.jiac.2022.03.027
PMID: 35428575 [Indexed for MEDLINE]

71. **Levofloxacin Use in Patients with Suspected Tuberculosis in a Community Hospital, Thailand: A Pilot Study.**

Adv Pharmacol Pharm Sci. 2022 Jun 3;2022:5647071. doi: 10.1155/2022/5647071.

eCollection 2022.

Khongyot T(1)(2), Laopaiboonkun S(1), Kawpradid T(1), Jitkamrop K(1), Chanphakphoom T(1), Uitrakul S(1).

BACKGROUND: Levofloxacin is one of the broad-spectrum antibiotics that is indicated for the second-line treatment of tuberculosis (TB). However, using levofloxacin as an empirical therapy for patients without confirmation of TB could still be observed. This descriptive retrospective study, therefore, aimed to investigate the number of levofloxacin use in patients suspected TB in a community hospital in Thailand.
METHODS: Patient medical charts of all patients who were admitted to a community hospital in Nakhon Si Thammarat, Thailand, from 2016 to 2017, were reviewed. Patients who were suspected TB and received any levofloxacin-containing regimens were included. Data on patient characteristics and the received regimens were descriptively analyzed and reported as percentage and frequency.
RESULTS: There were a total of 21 patients who received levofloxacin in the hospital. Six of them (28.57%) had the diagnosis of hepatitis. The most prescribed regimen as empirical therapy was levofloxacin, ethambutol, and amikacin (66.67%). After the confirmation of TB using acid-fast bacilli (AFB) test, ten patients (47.62%) still received levofloxacin-containing regimens.
CONCLUSION: The results from this study indicated high usage of levofloxacin despite no evidence of drug-resistant TB or negative AFB results in a community hospital in Thailand. The results from this study will be further used for the investigation of the prevalence of antibiotic resistance and clinical outcomes of using second-line regimens for TB treatment.

DOI: 10.1155/2022/5647071
PMCID: PMC9187489
PMID: 35692873

Conflict of interest statement: All authors have no conflicts of interest.

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

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

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

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

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

Conflict of interest statement: The authors declare no conflict of interest.

73. [**Study on the pharmacodynamic activity of combinations with the new anti-tuberculosis drug pyrifazimine in vitro and in vivo in mouse].**

[Article in Chinese; Abstract available in Chinese from the publisher]

Zhonghua Jie He He Hu Xi Za Zhi. 2022 Jun 12;45(6):560-566. doi: 10.3760/cma.j.cn112147-20211008-00697.

Liu HT(1), Fu L(1), Wang B(1), Wang N(1), Li DS(1), Ding YM(1), Yao R(1), Qi XT(1), Lu Y(1).

Objective: To evaluate two-drug combination interaction between pyrifazimine(TBI-166) and anti-drug-resistant tuberculosis group A drugs Bedaquiline (BDQ), Moxifloxacin (MFX) and the new anti-tuberculosis drug Delamanid (DLM), SQ109, Q203, and PBTZ169 in vitro and in vivo in mouse, so as to provide basis for TBI-166 combination therapy. Methods: This study was performed from September 2020 to July 2021. The chessboard method was used to evaluate the interaction between TBI-166 and BDQ, MFX, DLM, SQ109, and PBTZ169. The time-killing kinetics method was used to evaluate the anti-tuberculosis activity of the two-drug combination with partial synergy. The BALB/c mouse acute infection model was used to evaluate the anti-tuberculosis activity at 4 and 8 weeks in the two-drug combination group (TBI-166+BDQ, TBI-166+SQ109, TBI-166+PBTZ169, TBI-166+Q203) and monotherapy groups (TBI-166, BDQ, SQ109, PBTZ169, Q203). Data analysis was performed using an independent sample t-test. Results: After TBI-166 combined with anti-tuberculosis drugs, MIC was reduced to 6.25% to 25.00% of TBI-166 monotherapy. After TBI-166 combined with BDQ, SQ109 and PBTZ169, the partial inhibitory concentration index (FICI) values were 0.53, 0.75 and 0.75, respectively; the time sterilization experiment showed that the viable population of Mycobacterium tuberculosis treated with two-drug combination of TBI-166 and BDQ, SQ109, PBTZ169 for 14 days decreased at least 3 log10 CFU/ml. In the mouse experiments, it was found that, the amount of viable bacteria in lung tissue of BDQ, SQ109 and PBTZ169 combined with TBI-166 groups was lower than that of the monotherapy group,respectively. The lung tissue culture of mice in the TBI-166+BDQ group was negative after 4 weeks of treatment, and the number of live bacteria in the lungs of the TBI-166+BDQ group was 1.49 log10CFU lower than that of the BDQ monotherapy group($P<0.01$). Conclusion: In vitro and in vivo experiments in mice revealed that TBI-166 had synergistic anti-tuberculosis activity after being combined with BDQ, SQ109 and PBTZ169, respectively.

DOI: 10.3760/cma.j.cn112147-20211008-00697
PMID: 35658380 [Indexed for MEDLINE]

74. **Hearing aid support for patients with DR-TB in Ethiopia.**

Public Health Action. 2022 Jun 21;12(2):74-78. doi: 10.5588/pha.21.0068.

Teferra G(1), Teklemariam K(2), Wares DF(3), Negeri C(4), Bedru A(1).

SETTING: Previous and current patients with drug-resistant TB (DR-TB) who had

documented treatment-related hearing impairment due to second-line injectable (SLI) use were identified from different DR-TB treatment initiation centres in Ethiopia.
OBJECTIVE: To assess selected patients with DR-TB for eligibility for hearing aids and provide hearing aids to 10 eligible patients.
DESIGN: This was an observational cohort study. Patients were followed up for 8 months, with hearing assessments conducted at 1, 3 and 8 months to objectively assess hearing capacity.
RESULTS: Of 12 patients assessed for hearing aids eligibility, 10 were fitted with hearing aids (type XTM XP P4) and followed up for 8 months. "Formal" improvement was observed only in one patient. However, "general quality of life" appeared to be improved in nine patients.
CONCLUSION: Minimal "formal" improvement was observed. However, the study was too small to say whether hearing aids should, or should not, be recommended as a public health measure. This needs a larger better controlled follow-up study.
The all-oral DR-TB treatment regimens should be used for all patients with DR-TB in Ethiopia. However, as a proportion of patients with DR-TB are likely to continue receiving SLIs in the foreseeable future, they will require close audiometry assessment and appropriate care.

DOI: 10.5588/pha.21.0068
PMCID: PMC9176189
PMID: 35734010

75. **Impact of Rv0678 mutations on patients with drug-resistant TB treated with bedaquiline.**

Int J Tuberc Lung Dis. 2022 Jun 1;26(6):571-573. doi: 10.5588/ijtld.21.0670.

Kaniga K(1), Lounis N(2), Zhuo S(3), Bakare N(4), Andries K(2).

DOI: 10.5588/ijtld.21.0670
PMCID: PMC9165736
PMID: 35650698 [Indexed for MEDLINE]

76. **[Exploratory study on detection of drug resistance of Mycobacterium tuberculosis in sputum specimens by next-generation sequencing].**

[Article in Chinese; Abstract available in Chinese from the publisher]

Zhonghua Jie He He Hu Xi Za Zhi. 2022 Jun 12;45(6):552-559. doi:

10.3760/cma.j.cn112147-20211104-00775.

Liu YY(1), Shi J(2), Chu P(1), Wu TY(3), Li L(4), Pang Y(4), Lu J(1), Guo YL(1).

Objective: To compare the diagnostic performance of next-generation sequencing (NGS) detection methods in sputum samples and Mycobacterium tuberculosis strains, in order to explore the feasibility of the NGS method to detect drug resistance in sputum specimens. Methods: In this retrospective study, the sputum specimens and corresponding clinical isolates of 50 pulmonary tuberculosis patients admitted to Beijing Chest Hospital from January 2017 to December 2017 were collected. The gene mutations of katG, inhA, rpoB, embA, embB, rpsL, rrs, gyrA, gyrB and tlyA in sputum specimens and corresponding clinical isolates were detected by NGS method. The phenotypic drug susceptibility test (DST) of the strains was carried out by the proportion method. Using DST results as a reference, the sensitivity, specificity, positive predictive value and negative predictive value of the NGS method for clinical strains and sputum specimens, as well as the consistency statistic (Kappa) with phenotype DST were calculated respectively. The Chi-square test was used to compare the accuracy of the NGS testing in sputum samples and strain samples. Results: The results showed that rpoB(63.83%, 30/47) and rrs(57.45%, 27/47) were the most common mutated genes, followed by katG(46.81%, 22/47), rpsL(29.79%, 14/47), gyrA(27.66%, 13/47), embB(21.28%, 10/47), tlyA(12.77%, 6/47), gyrB(8.51%, 4/47), and inhA promoter(19.15%, 9/47), embA promoter region (12.77%, 6/47) mutation. when the NGS method was compared with the resistance phenotype of isoniazid, rifampicin, ethambutol, second-line injectable drugs (streptomycin, capreomycin, kanamycin, amikacin), levofloxacin, the sensitivity were 85.71%, 91.67%, 77.78%, 81.82%, 100.00%, 87.50%, 100.00%, 69.23%, and the specificity were 100.00%, 94.12, 87.50%, 89.47%, 97.06%, 96.97%, 94.29%, 89.29% in sputum samples, while in strain samples, the sensitivity were 92.86%, 100.00%, 81.82%, 86.96%, 88.89%, 80.00%, 100.00%, 85.71%. The specificity were 100.00%, 92.86%, 87.10%, 94.74%, 100.00%, 100.00%, 97.14%, 92.86%. Compared with the phenotypic drug susceptibility results, the NGS method has better detection performance for isoniazid, rifampicin, capreomycin, kanamycin, and amikacin in sputum specimens (Kappa≥0.75); while among the strains, the NGS method had a good detection performance for isoniazid, rifampicin, streptomycin, capreomycin, kanamycin, amikacin and levofloxacin (Kappa≥0.75). With the accuracy of the NGS method for detecting strains as a reference, there was no statistically significant difference in the accuracy of all drug resistance detected between strains and sputum specimens. Conclusions: This study showed that the NGS technology was effective in predicting the resistance of isoniazid, rifampicin, and second-line injectable drugs (capreomycin, kanamycin and amikacin) by detecting sputum samples and strain genotypes, suggesting the feasibility and potential of direct detection of sputum samples by the NGS method as an early detection method for drug resistance.

DOI: 10.3760/cma.j.cn112147-20211104-00775
PMID: 35658379 [Indexed for MEDLINE]

77. **GSK2556286 Is a Novel Antitubercular Drug Candidate Effective In Vivo with the Potential To Shorten Tuberculosis Treatment.**

Antimicrob Agents Chemother. 2022 Jun 21;66(6):e0013222. doi: 10.1128/aac.00132-22. Epub 2022 May 24.

Nuermberger EL(1), Martínez-Martínez MS(2), Sanz O(2), Urones B(2), Esquivias J(2), Soni H(1), Tasneen R(1), Tyagi S(1), Li SY(1), Converse PJ(1), Boshoff HI(3), Robertson GT(4), Besra GS(5), Abrahams KA(5), Upton AM(6), Mdluli K(6), Boyle GW(7), Turner S(7), Fotouhi N(6), Cammack NC(2), Siles JM(2), Alonso M(2), Escribano J(2), Lelievre J(2), Rullas-Trincado J(2), Pérez-Herrán E(2), Bates RH(2), Maher-Edwards G(8), Barros D(2), Ballell L(2), Jiménez E(2).

As a result of a high-throughput compound screening campaign using Mycobacterium tuberculosis-infected macrophages, a new drug candidate for the treatment of tuberculosis has been identified. GSK2556286 inhibits growth within human macrophages (50% inhibitory concentration [IC50] = 0.07 μM), is active against extracellular bacteria in cholesterol-containing culture medium, and exhibits no cross-resistance with known antitubercular drugs. In addition, it has shown efficacy in different mouse models of tuberculosis (TB) and has an adequate safety profile in two preclinical species. These features indicate a compound with a novel mode of action, although still not fully defined, that is effective against both multidrug-resistant (MDR) or extensively drug-resistant (XDR) and drug-sensitive (DS) M. tuberculosis with the potential to shorten the duration of treatment in novel combination drug regimens. (This study has been registered at ClinicalTrials.gov under identifier NCT04472897).

DOI: 10.1128/aac.00132-22
PMCID: PMC9211396
PMID: 35607978 [Indexed for MEDLINE]

Conflict of interest statement: The authors declare a conflict of interest. Maria Santos Martínez-Martínez, Jorge Esquivias, Juan Miguel Siles, Marta Alonso, Jaime Escribano, Joaquin Rullas-Trincado, Esther Pérez-Herrán, Gareth Maher-Edwards, Joel Lelievre, Elena Jimenez, Olalla Sanz, Gary Boyle, Sam Turner, Beatriz Urones, Robert H. Bates, David Barros, are employees of GlaxoSmithKline. Eric L. Nuermberger receives research support from Janssen and the TB Alliance.

78. **Uncovering Beta-Lactam Susceptibility Patterns in Clinical Isolates of**

June 27th, 2022

Mycobacterium tuberculosis through Whole-Genome Sequencing.

Microbiol Spectr. 2022 Jun 13:e0067422. doi: 10.1128/spectrum.00674-22. Online ahead of print.

Olivença F(1), Nunes A(2), Macedo R(3), Pires D(1), Silveiro C(1), Anes E(1), Miragaia M(4), Gomes JP(2), Catalão MJ(1).

The increasing threat of drug resistance and a stagnated pipeline of novel therapeutics endanger the eradication of tuberculosis. Beta-lactams constitute promising additions to the current therapeutic arsenal and two carbapenems are included in group C of medicines recommended by the WHO for use in longer multidrug-resistant tuberculosis regimens. However, the determinants underlining diverse Mycobacterium tuberculosis phenotypes to beta-lactams remain largely undefined. To decipher these, we present a proof-of-concept study based on a large-scale beta-lactam susceptibility screening for 172 M. tuberculosis clinical isolates from Portugal, including 72 antimycobacterial drug-resistant strains. MICs were determined for multiple beta-lactams and strains were subjected to whole-genome sequencing to identify core-genome single-nucleotide variant-based profiles. Global and cell wall-targeted approaches were then followed to detect putative drivers of beta-lactam response. We found that drug-resistant strains were more susceptible to beta-lactams, but significant differences were not observed between distinct drug-resistance profiles. Sublineage 4.3.4.2 strains were significantly more susceptible to beta-lactams, while the contrary was observed for Beijing and 4.1.2.1 sublineages. While mutations in beta-lactamase or cell wall biosynthesis genes were uncommon, a rise in beta-lactam MICs was detected in parallel with the accumulation of mutations in peptidoglycan cross-linking or cell division genes. Finally, we exposed that putative beta-lactam resistance markers occurred in genes for which relevant roles in cell wall processes have been ascribed, such as rpfC or pknA. Genetic studies to validate the relevance of the identified mutations for beta-lactam susceptibility and further improvement of the phenotype-genotype associations are needed in the future. IMPORTANCE Associations between differential M. tuberculosis beta-lactam phenotypes and preexisting antimycobacterial drug resistance, strain sublineage, or specific mutational patterns were established. Importantly, we reveal that highly drug-resistant isolates of sublineage 4.3.4.2 have an increased susceptibility to beta-lactams compared with other strains. Thus, directing beta-lactams to treat infections by specific M. tuberculosis strains and refraining its use from others emerges as a potentially important strategy to avoid resistance development. Individual mutations in blaC or genes encoding canonical beta-lactam targets, such as peptidoglycan transpeptidases, are infrequent and do not greatly impact the MICs of potent carbapenem plus clavulanic acid combinations. An improved understanding of the global effect of cumulative mutations in relevant gene sets

for peptidoglycan and cell division processes on beta-lactam susceptibility is also provided.

DOI: 10.1128/spectrum.00674-22
PMID: 35695524

79. **Corrigendum to 'Culture conversion at six months in patients receiving bedaquiline- and delamanid-containing regimens for the treatment of multidrug-resistant tuberculosis' International Journal of Infectious Diseases Volume 113S1 (2021) S91-S95.**

Int J Infect Dis. 2022 Aug;121:105. doi: 10.1016/j.ijid.2022.05.004. Epub 2022 May 23.

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).

Erratum for
Int J Infect Dis. 2021 Dec;113 Suppl 1:S91-S95.

DOI: 10.1016/j.ijid.2022.05.004
PMID: 35613479

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

Vasc Med. 2022 Jun;27(3):308-309. doi: 10.1177/1358863X211056681. Epub 2021 Nov 22.

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

DOI: 10.1177/1358863X211056681
PMID: 34802310 [Indexed for MEDLINE]

81. **Whole Genome Sequencing Identifies Novel Mutations Associated With Bedaquiline Resistance in Mycobacterium tuberculosis.**

Front Cell Infect Microbiol. 2022 May 27;12:807095. doi: 10.3389/fcimb.2022.807095. eCollection 2022.

Guo Q(1), Bi J(1), Lin Q(2), Ye T(1), Wang Z(1), Wang Z(1), Liu L(1), Zhang G(1).

Bedaquiline (BDQ), a new antitubercular agent, has been used to treat drug-resistant tuberculosis (TB). Although mutations in atpE, rv0678, and pepQ confer major resistance to BDQ, the mechanisms of resistance to BDQ in vitro and in clinical settings have not been fully elucidated. We selected BDQ-resistant mutants from 7H10 agar plates containing 0.5 mg/L BDQ (the critical concentration) and identified mutations associated with BDQ resistance through whole genome sequencing and Sanger sequencing. A total of 1,025 mutants were resistant to BDQ. We randomly selected 168 mutants for further analysis and discovered that 157/168 BDQ-resistant mutants harbored mutations in rv0678, which encodes a transcriptional regulator that represses the expression of the efflux pump, MmpS5-MmpL5. Moreover, we found two mutations with high frequency in rv0678 at nucleotide positions 286-287 (CG286-287 insertion; accounting for 26.8% [45/168]) and 198-199 (G198, G199 insertion, and G198 deletion; accounting for 14.3% [24/168]). The other mutations were dispersed covering the entire rv0678 gene. Moreover, we found that one new gene, glpK, harbors a G572 insertion; this mutation has a high prevalence (85.7%; 144/168) in the isolated mutants, and the minimum inhibitory concentration (MIC) assay demonstrated that it is closely associated with BDQ resistance. In summary, we characterized 168/1,025 mutants resistant to BDQ and found that mutations in rv0678 confer the primary mechanism of BDQ resistance. Moreover, we identified a new gene (glpK) involved in BDQ resistance. Our study offers new insights and valuable information that will contribute to rapid identification of BDQ-resistant isolates in clinical settings.

DOI: 10.3389/fcimb.2022.807095
PMCID: PMC9184757
PMID: 35694543 [Indexed for MEDLINE]

Conflict of interest statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

82. **Assessing the QTcF prolongation of bedaquiline and delamanid coadministration to predict the cardiac safety of simplified dosing regimens.**

Clin Pharmacol Ther. 2022 Jun 10. doi: 10.1002/cpt.2685. Online ahead of print.

Tanneau L(1), Karlsson MO(1), Rosenkranz SL(2), Cramer YS(2), Shenje J(3), Upton CM(4), Morganroth J(5), Diacon AH(4), Maartens G(6), Dooley KE(7), Svensson EM(1)(8).

Delamanid and bedaquiline are two drugs approved to treat drug-resistant tuberculosis, and each have been associated with QTc prolongation. We aimed to investigate the relationships between the drugs' plasma concentrations and observed QTcF prolongation and to evaluate their combined effects on QTcF, using a model-based population approach. Furthermore, we predicted the safety profiles of once daily regimens. Data were obtained from a trial where participants were randomized 1:1:1 to receive delamanid, bedaquiline or delamanid+bedaquiline. The effect on QTcF of delamanid and/or its metabolite (DM-6705) and the pharmacodynamic interactions under co-administration, were explored based on a published model between bedaquiline's metabolite (M2) and QTcF. The metabolites of each drug were found to be responsible for the drug-related QTcF prolongation. The final drug-effect model included a competitive interaction between M2 and DM-6705 acting on the same cardiac receptor and thereby reducing each other's apparent potency, by 28% (95CI 22%-40%) for M2 and 33% (95CI 24%-54%) for DM-6705. The generated combined effect was not greater but close to "additivity" in the analysed concentration range. Predictions with the final model suggested a similar QT prolonging potential with simplified, once daily dosing regimens compared to the approved regimens, with a maximum median change from baseline QTcF increase of 20 ms in both regimens. The concentrations-QTcF relationship of the combination of bedaquiline and delamanid was best described by a competitive binding model involving the two main metabolites. Model predictions demonstrated that QTcF prolongation with simplified once daily regimens would be comparable to currently used dosing regimens.

DOI: 10.1002/cpt.2685
PMID: 35687528

83. **Molecular detection of isoniazid monoresistance improves tuberculosis treatment: A retrospective cohort in France.**

J Infect. 2022 Jul;85(1):24-30. doi: 10.1016/j.jinf.2022.05.017. Epub 2022 May 20.

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) requires early diagnosis and adapted treatment to achieve optimal outcomes. The primary aim of the study was to assess the impact of the implementation of rapid diagnostic tests on HR-TB treatment in France.

METHODS: We designed a retrospective multicentre study including consecutive HR-TB patients diagnosed in 2016 and 2017. Implementation of a molecular assay detecting isoniazid resistance directly on a clinical sample was recorded. The association between early implementation of such assays and adequate treatment was assessed by a multivariable Cox proportional hazards model.
RESULTS: Overall, 99 HR-TB patients were included from 20 University Hospitals. Among all smear-positive HR-TB patients, only 26% beneficiated from early molecular HR detection. This detection was independently associated with shorter time to adequate treatment (HR = 2.0 [1.1-3.8], p = 0.03).
CONCLUSION: In our study, molecular detection of HR on an initial sample was independently associated with earlier treatment adaptation.

DOI: 10.1016/j.jinf.2022.05.017
PMID: 35605802 [Indexed for MEDLINE]

Conflict of interest statement: Declaration of Competing Interest None.

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

Infect Genet Evol. 2022 Jul;101:105288. doi: 10.1016/j.meegid.2022.105288. Epub 2022 Apr 27.

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

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

assess the role of novel mutations was also performed. Our findings highlight the importance of detecting discrete intra-host populations carrying DR mutations.

DOI: 10.1016/j.meegid.2022.105288
PMID: 35489699 [Indexed for MEDLINE]

85. **Early line-probe assay using DNA specimens in patients with pulmonary TB.**

Int J Tuberc Lung Dis. 2022 Jun 1;26(6):509-515. doi: 10.5588/ijtld.21.0381.

Shin AY(1), Jekarl DW(2), Kim HW(1), Ha JH(1), Ahn JH(1), Kim JS(1).

BACKGROUND: We investigated the feasibility of early line-probe assay (LPA) using remnant DNA of Mycobacterium tuberculosis from polymerase chain reaction (PCR) test.METHODS: M. tuberculosis DNA specimens with cycle threshold (Ct) values reported and collected from patients with known results for both LPA with culture isolates and phenotype drug susceptibility testing (pDST) were selected. The diagnostic performance of DNA-based LPA according to the Ct value was investigated.RESULTS: A total of 143 respiratory specimens were included. For isoniazid resistance, the accuracy in subgroups with Ct value <25, 25-29 and ≥29 was respectively 96.8%, 65.7% and 13.3%. For rifampicin resistance, accuracy in subgroups with Ct values <29 and ≥29 was respectively 87.8% and 13.3%. When compared to the pDST results, sensitivity, specificity, positive predictive value and negative predictive value in specimens with Ct values <25 was respectively 1.00 (95% CI 0.69-1.00), 0.95 (95% CI 0.76-1.00), 0.91 (95% CI 0.59-1.00) and 1.00 (95% CI 0.83-1.00) for isoniazid resistance. For rifampicin resistance, corresponding values in subgroups with Ct values <29 were respectively 0.89 (95% CI 0.52-1.00), 0.98 (95% CI 0.91-1.00), 0.80 (95% CI 0.50-0.94) and 0.99 (95% CI 0.92-1.00).CONCLUSIONS: DNA-based early LPA with remnant DNA from respiratory samples was feasible and accurate when the Ct values were low.

DOI: 10.5588/ijtld.21.0381
PMID: 35650694 [Indexed for MEDLINE]

86. **In vitro activity of tedizolid and linezolid against multidrug-resistant Mycobacterium tuberculosis: a comparative study using microdilution broth assay and genomics.**

Diagn Microbiol Infect Dis. 2022 Jul;103(3):115714. doi: 10.1016/j.diagmicrobio.2022.115714. Epub 2022 Apr 22.

Aono A(1), Murase Y(2), Chikamatsu K(2), Igarashi Y(2), Shimomura Y(2), Hosoya M(2), Osugi A(2), Morishige Y(2), Takaki A(2), Yamada H(2), Mitarai S(3).

The effects of tedizolid (TZD) against multidrug-resistant Mycobacterium tuberculosis isolates were investigated. This is possibly the first study to evaluate the MIC of TZD against Japanese Mycobacterium tuberculosis isolates. As TZD had a significantly lower MIC than LZD ($P < 0.01$), it was suggested to be a better, non-toxic alternative to LZD.

DOI: 10.1016/j.diagmicrobio.2022.115714
PMID: 35596983 [Indexed for MEDLINE]

Conflict of interest statement: Declaration of competing interest The authors declare no conflict of interest.

87. **Adapting Clofazimine for Treatment of Cutaneous Tuberculosis by Using Self-Double-Emulsifying Drug Delivery Systems.**

Antibiotics (Basel). 2022 Jun 15;11(6):806. doi: 10.3390/antibiotics11060806.

van Staden D(1), Haynes RK(1), Viljoen JM(1).

Although chemotherapeutic treatment regimens are currently available, and considerable effort has been lavished on the development of new drugs for the treatment of tuberculosis (TB), the disease remains deeply intractable and widespread. This is due not only to the nature of the life cycle and extraordinarily disseminated habitat of the causative pathogen, principally Mycobacterium tuberculosis (Mtb), in humans and the multi-drug resistance of Mtb to current drugs, but especially also to the difficulty of enabling universal treatment of individuals, immunocompromised or otherwise, in widely differing socio-economic environments. For the purpose of globally eliminating TB by 2035, the World Health Organization (WHO) introduced the "End-TB" initiative by employing interventions focusing on high impact, integrated and patient-centered approaches, such as individualized therapy. However, the extraordinary shortfall in stipulated aims, for example in actual treatment and in TB preventative treatments during the period 2018-2022, latterly and greatly exacerbated by the COVID-19 pandemic, means that even greater pressure is now placed on enhancing our scientific understanding of the disease, repurposing or repositioning old drugs and developing new drugs as well as evolving innovative treatment methods.

In the specific context of multidrug resistant Mtb, it is furthermore noted that the incidence of extra-pulmonary TB (EPTB) has significantly increased. This review focusses on the potential of utilizing self-double-emulsifying drug delivery systems (SDEDDSs) as topical drug delivery systems for the dermal route of administration to aid in treatment of cutaneous TB (CTB) and other mycobacterial infections as a prelude to evaluating related systems for more effective treatment of CTB and other mycobacterial infections at large. As a starting point, we consider here the possibility of adapting the highly lipophilic riminophenazine clofazimine, with its potential for treatment of multi-drug resistant TB, for this purpose. Additionally, recently reported synergism achieved by adding clofazimine to first-line TB regimens signifies the need to consider clofazimine. Thus, the biological effects and pharmacology of clofazimine are reviewed. The potential of plant-based oils acting as emulsifiers, skin penetration enhancers as well as these materials behaving as anti-microbial components for transporting the incorporated drug are also discussed.

DOI: 10.3390/antibiotics11060806
PMCID: PMC9219976
PMID: 35740212

Conflict of interest statement: The authors have no conflict of interest to declare.

88. **Evaluation of a novel inhibitor of aspartate semialdehyde dehydrogenase as a potent antitubercular agent against Mycobacterium tuberculosis.**

J Antibiot (Tokyo). 2022 Jun;75(6):333-340. doi: 10.1038/s41429-022-00520-y. Epub 2022 Apr 14.

Yang R(1), Cao W(2), Liu S(3), Li Q(1), Sun Y(4), Liang C(1), Ren W(1), Liu Y(1), Meng J(5), Li C(6).

The in vitro activity of IMB-XMA0038, a novel inhibitor targeting Mycobacterial tuberculosis (Mtb) aspartate semialdehyde dehydrogenase, was evaluated. Minimum inhibitory concentrations (MICs) of IMB-XMA0038 were against 20 Mtb isolates, including H37Rv (ATCC 27294), ten clinical pan-sensitive isolates, and nine clinical multidrug-resistant (MDR) isolates. In addition, minimum bactericidal concentrations (MBCs) were also determined against the H37Rv and 6 MDR isolates (the background information is same as above in order). A model was generated to evaluate IMB-XMA0038 activity against dormant Mtb. The post-antibiotic effect (PAE), an important indicator of antimicrobial drug dosing schedules to obtain efficacy, was determined based on time required for regrowth of Mtb to 50% of the OD600max value after treatment with various concentrations of IMB-XMA0038

and INH. In addition, interactions between IMB-XMA0038 and other anti-tuberculosis drugs, measured using a checkerboard assay, revealed that IMB-XMA0038 MICs of 0.5-1 μg/mL could be achieved in combinations. Synergistic effects were observed for IMB-XMA0038 when used together with almost all other anti-tuberculosis drugs against most Mtb isolates. IMB-XMA0038 exhibited greater activity than rifampin against Mtb under hypoxic conditions, as reflected by CFU decreases of 1.1-log-unit versus 0.8-log-unit, respectively, for IMB-XMA0038 and rifampin concentrations of 4 × MIC. IMB-XMA0038-induced PAEs (9, 10, 11 days) were comparable to INH PAEs (10, 11, 12 days). These findings suggest that addition of IMB-XMA0038 to current therapeutic regimens could be useful to improve the efficacy of treatments for drug-resistant and drug-susceptible TB.

DOI: 10.1038/s41429-022-00520-y
PMID: 35422103 [Indexed for MEDLINE]

89. **Pharmacokinetic-pharmacodynamic determinants of clinical outcomes for rifampin-resistant tuberculosis: a multi-site prospective cohort study.**

Clin Infect Dis. 2022 Jun 22:ciac511. doi: 10.1093/cid/ciac511. Online ahead of print.

Heysell SK(1), Mpagama SG(2)(3), Ogarkov OB(4), Conaway M(5), Ahmed S(6), Zhdanova S(4), Pholwat S(1), Alshaer MH(7), Chongolo AM(2), Mujaga B(3), Sariko M(3), Saba S(6), Rahman SMM(6), Uddin MKM(6), Suzdalnitsky A(8), Moiseeva E(8), Zorkaltseva E(9), Koshcheyev M(8), Vitko S(1), Mmbaga BT(3), Kibiki GS(3), Pasipanodya JG(10), Peloquin CA(7), Banu S(6), Houpt ER(1).

BACKGROUND: Treatment of rifampin-resistant and/or multidrug-resistant tuberculosis (RR/MDR-TB) requires multiple drugs and outcomes remain suboptimal. Some drugs are associated with improved outcome, however whether particular pharmacokinetic-pharmacodynamic relationships predict outcome is unknown. METHODS: Adults with pulmonary RR/MDR-TB in Tanzania, Bangladesh and Russian Federation receiving therapy with local regimens were enrolled from June, 2016 to July, 2018. Serum was collected after two, four, and eight weeks for each drug's area under the concentration-time curve (AUC0-24) and quantitative susceptibility of the Mycobacterium tuberculosis isolate measured by minimum inhibitory concentrations (MIC). Individual drug AUC0-24/MIC targets were assessed by adjusted odds ratios (OR) for association with favorable treatment outcome and hazard ratios (HR) for time to sputum culture conversion. K-means clustering algorithm separated the cohort of the most common multidrug regimen

into four clusters by AUC0-24/MIC exposures.
RESULTS: Among 290 patients, 62 (21%) experienced treatment failure, including 30 deaths. Moxifloxacin AUC0-24/MIC target of 58 was associated with favorable treatment outcome [OR 3.75 (1.21, 11.56), p = 0·022], while levofloxacin AUC0-24/MIC of 118.3, clofazimine AUC0-24/MIC of 50.5, and pyrazinamide AUC0-24 of 379 mg*h/L were associated with faster culture conversion [HR > 1·0, p < 0.05]. Other individual drug exposures were not predictive. Clustering by AUC0-24/MIC revealed those with lowest multidrug exposures had slowest culture conversion.
CONCLUSION: Amidst multidrug regimens for RR/MDR-TB, serum pharmacokinetics and M. tuberculosis MICs were variable, yet defined parameters to certain drugs - fluoroquinolones, pyrazinamide, clofazimine - were predictive and should be optimized to improve clinical outcome.

DOI: 10.1093/cid/ciac511
PMID: 35731948

90. **Risk-adjusted active tuberculosis case finding strategy in central Ethiopia.**

IJID Reg. 2022 Mar 20;3:196-203. doi: 10.1016/j.ijregi.2022.03.012. eCollection 2022 Jun.

Fuchs A(1)(2), Tufa TB(1)(3)(4), Pfäfflin F(5), Schönfeld A(6), Nordmann T(7), Melaku F(8), Sorsa A(3), Orth HM(1)(4), Häussinger D(1)(4), Luedde T(1)(4), Feldt T(1)(4).

BACKGROUND: The World Health Organization recommends active case finding for tuberculosis (TB). Our study evaluated the targeted screening of household contacts (HHCs) of patients with contagious pulmonary tuberculosis (PTB) in Central Ethiopia.
METHODS: The HHCs of patients with microbiologically confirmed PTB were screened for TB symptoms and risk factors for TB transmission. Symptomatic HHCs were subjected to secondary investigation. Antimicrobial resistance was investigated among study participants.
RESULTS: Overall, 112 index patients with TB were included, and 289 HHCs from 89 households were screened. Multidrug-resistant-TB was detected in 2.7% (n=3) of index patients. The routine public health system process did not identify any TB suspects among HHCs. In total, 23.9% (n=69) of HHCs reported ≥1 TB symptom and PTB was confirmed in 2.1% (n=6). Reporting >1 TB symptom (relative risk [RR] 29.4, 95% CI 3.5-245.5, P<0.001) and night sweats (RR 27.1, 95% CI 3.2-226.6, P<0.001) were associated with the greatest relative risk. Regular alcohol

consumption was identified as an individual risk factor for TB among HHCs (P=0.022).
CONCLUSION: The MDR-TB rate among our patients was higher than recently reported for Ethiopia. Enhanced contact tracing using a risk-adjusted approach seems feasible and increases the case detection rate among HHCs of confirmed TB cases.

DOI: 10.1016/j.ijregi.2022.03.012
PMCID: PMC9216629
PMID: 35755475

Conflict of interest statement: All authors declare that they have no conflicts of interest.

91. **Development, validation and clinical use of a LC-MS/MS method for the simultaneous determination of the nine main antituberculosis drugs in human plasma.**

J Pharm Biomed Anal. 2022 Jun 5;215:114776. doi: 10.1016/j.jpba.2022.114776. Epub 2022 Apr 19.

Fage D(1), Brilleman R(2), Deprez G(3), Payen MC(4), Cotton F(3).

The treatment of tuberculosis, in particular the multi-drug resistant tuberculosis, remains a challenge mainly because of the therapy duration and the pharmacokinetic variability of the drugs included in the regimen. The monitoring of antituberculosis drugs is a recent tool that could improve the outcome of patients. We developed a LC-MS/MS method allowing the simultaneous quantification of the four first-line drugs (isoniazid, rifampicin, pyrazinamide and ethambutol), a metabolite of isoniazid (acetylisoniazid) and the five main second-line drugs (rifabutin, levofloxacin, moxifloxacin, linezolid and bedaquiline). An isotopologue standard was used for each drug. The protein precipitation was performed with acetonitrile and the separation was carried out using an EC-18 column and a gradient elution. The validated ranges for each drug were adapted to monitor the plasma concentration at 2 h (peak) and 6 h to evaluate their enteric absorption. The intermediate precision (CV) and the trueness at the limit of quantification were ≤ 10.1% and ≤ 10.7%, respectively. Preliminary data were obtained for 12 patients. The results showed that 38% of the patients had infra-therapeutic levels for both rifampicin and isoniazid, that the leading cause of an impaired oral absorption seemed to be malabsorption and that the effective concentrations for rifampicin were in the lower range of the therapeutic interval.

DOI: 10.1016/j.jpba.2022.114776
PMID: 35462286 [Indexed for MEDLINE]

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

J Infect Chemother. 2022 Aug;28(8):1193-1197. doi: 10.1016/j.jiac.2022.04.028. Epub 2022 May 10.

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

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

DOI: 10.1016/j.jiac.2022.04.028
PMID: 35550867 [Indexed for MEDLINE]

93. **Minimum inhibitory concentration of cycloserine against Mycobacterium tuberculosis using the MGIT 960 system and a proposed critical concentration.**

Int J Infect Dis. 2022 Aug;121:148-151. doi: 10.1016/j.ijid.2022.05.030. Epub

2022 May 13.

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

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

DOI: 10.1016/j.ijid.2022.05.030
PMID: 35577251 [Indexed for MEDLINE]

Conflict of interest statement: Conflict of interest The authors have no conflict of interests to declare.

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

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

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

Ciprofloxacin (CPX), a second generation fluoroquinolone antibiotic, is used as a primary antibiotic for treatment against gastroenteritis, drug-resistant tuberculosis, and malignant otitis externa. CPX is a broad spectrum antibiotic

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

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

95. **Resistance and tolerance of Mycobacterium tuberculosis to antimicrobial agents-How M. tuberculosis can escape antibiotics.**

WIREs Mech Dis. 2022 Jun 26:e1573. doi: 10.1002/wsbm.1573. Online ahead of print.

Li H(1), Yuan J(1), Duan S(2), Pang Y(1).

Tuberculosis (TB) poses a serious threat to public health worldwide since it was discovered. Until now, TB has been one of the top 10 causes of death from a single infectious disease globally. The treatment of active TB cases majorly relies on various anti-tuberculosis drugs. However, under the selection pressure by drugs, the continuous evolution of Mycobacterium tuberculosis (Mtb) facilitates the emergence of drug-resistant strains, further resulting in the accumulation of tubercle bacilli with multiple drug resistance, especially deadly multidrug-resistant TB and extensively drug-resistant TB. Researches on

the mechanism of drug action and drug resistance of Mtb provide a new scheme for clinical management of TB patients, and prevention of drug resistance. In this review, we summarized the molecular mechanisms of drug resistance of existing anti-TB drugs to better understand the evolution of drug resistance of Mtb, which will provide more effective strategies against drug-resistant TB, and accelerate the achievement of the EndTB Strategy by 2035. This article is categorized under: Infectious Diseases > Molecular and Cellular Physiology.

DOI: 10.1002/wsbm.1573
PMID: 35753313

96. **Keeping up with the guidelines: design changes to the STREAM stage 2 randomised controlled non-inferiority trial for rifampicin-resistant tuberculosis.**

Trials. 2022 Jun 7;23(1):474. doi: 10.1186/s13063-022-06397-4.

Goodall RL(1), Sanders K(2), Bronson G(3), Gurumurthy M(4), Torrea G(5), Meredith S(2), Nunn A(2), Rusen ID(3); STREAM Trial Team.

Collaborators: Bronson G, Gurumurthy M, Komrska J, Patel L, Qawiy I, Rusen ID, Ali S, Bellenger K, Bennet D, Bennet R, Dodds W, Goodall R, Meredith S, Murphy B, Nunn A, Roach C, Sanders K, Whitney J, Van Deun A, Torrea G, Chiang CY, Rosu L, Squire B, Madan J.

Results from the STREAM stage 1 trial showed that a 9-month regimen for patients with rifampicin-resistant tuberculosis was non-inferior to the 20-month regimen recommended by the 2011 WHO treatment guidelines. Similar levels of severe adverse events were reported on both regimens suggesting the need for further research to optimise treatment. Stage 2 of STREAM evaluates two additional short-course regimens, both of which include bedaquiline. Throughout stage 2 of STREAM, new drug choices and a rapidly changing treatment landscape have necessitated changes to the trial's design to ensure it remains ethical and relevant. This paper describes changes to the trial design to ensure that stage 2 continues to answer important questions. These changes include the early closure to recruitment of two trial arms and an adjustment to the definition of the primary endpoint. If the STREAM experimental regimens are shown to be non-inferior or superior to the stage 1 study regimen, this would represent an important contribution to evidence about potentially more tolerable and more efficacious MDR-TB regimens, and a welcome advance for patients with rifampicin-resistant tuberculosis and tuberculosis control programmes globally.Trial registration: ISRCTN ISRCTN18148631 . Registered 10 February

2016.

DOI: 10.1186/s13063-022-06397-4
PMCID: PMC9171092
PMID: 35672833 [Indexed for MEDLINE]

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

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

Environ Sci Pollut Res Int. 2022 Jun;29(27):40542. doi: 10.1007/s11356-022-20415-7.

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

Erratum for
Environ Sci Pollut Res Int. 2022 Jun;29(27):40531-40541.

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

98. **Causes of loss to follow-up from drug-resistant TB treatment in Khayelitsha, South Africa.**

Public Health Action. 2022 Jun 21;12(2):55-57. doi: 10.5588/pha.21.0083.

Memani B(1), Beko B(1), Dumile N(1), Mohr-Holland E(1)(2), Daniels J(1), Sibanda B(1), Damse Z(3), Scott V(3), von der Heyden E(4), Pfaff C(1), Reuter A(1), Furin J(5).

Patients initiated on drug-resistant TB(DR-TB) treatment in 2019 in Khayelitsha, South Africa, with a loss to follow-up outcome were evaluated to better understand reasons for loss to follow-up and to determine if any had returned to care. Of a total of 187 patients, 28 (15%) were lost to follow-up (LTFU), 24 (86%) of whom were traced: 20/24 (83%) were found when they re-presented to facilities and 8/28 (29%) were linked back to DR-TB care. People with DR-TB

continue to seek care even after being LTFU; thus better coordination between different components of the healthcare system are required to re-engage with these patients. Interventions to mitigate the socio-economic challenges of people on DR-TB treatment are needed. Many people who were LTFU and symptomatic were willing to re-engage with DR-TB care, which highlights the importance of for compassionate interventions to welcome them back.

DOI: 10.5588/pha.21.0083
PMCID: PMC9176197
PMID: 35734003

99. **Recurrent pneumothorax in a human immunodeficiency virus-positive patient with multidrug-resistant tuberculosis: a rare case of bronchopleural fistula: a case report.**

J Med Case Rep. 2022 May 31;16(1):214. doi: 10.1186/s13256-022-03436-1.

Nakiyingi L(1)(2), Baluku JB(3), Ssengooba W(4)(5), Namiiro SM(5), Buyego P(6), Kimuli I(7)(5), Adakun S(3).

BACKGROUND: Human immunodeficiency virus/tuberculosis coinfections have amplified the multidrug-resistant tuberculosis pandemic in many countries in Sub-Saharan Africa, and multidrug-resistant tuberculosis has become a major public health threat. There is a paucity of data on severe complications of multidrug-resistant tuberculosis in the context of human immunodeficiency virus coinfection despite the increasing prevalence of multidrug-resistant tuberculosis/human immunodeficiency virus coinfection and the complexity of multidrug-resistant tuberculosis treatment. This report describes a rare case of complicated multidrug-resistant tuberculosis in a human immunodeficiency virus-positive individual.
CASE PRESENTATION: A 39-year-old human immunodeficiency virus-positive Ugandan male on anti-retroviral therapy for 6 years, who had recently completed treatment for drug-susceptible tuberculosis from a public hospital, presented to the tuberculosis ward of Mulago National Referral Hospital with worsening respiratory symptoms including persistent cough with purulent sputum, fever, right chest pain, and shortness of breath. On admission, a diagnosis of drug-resistant tuberculosis was made following a positive sputum Xpert MTB/Rif test with rifampicin resistance. Culture-based tuberculosis tests and line probe assay confirmed multidrug-resistant tuberculosis. The patient was given multidrug-resistant tuberculosis treatment that included bedaquiline, isoniazid, prothionamide, clofazimine, ethambutol, levofloxacin, and pyrazinamide and

switched to second-line anti-retroviral therapy that included tenofovir/lamivudine/lopinavir/ritonavir. Chest X-ray revealed a hydro-pneumothorax, following which a chest tube was inserted. With persistent bubbling from the chest tube weeks later and a check chest X-ray that showed increasing pleural airspace (pneumothorax) and appearance of a new air-fluid level, chest computed tomography scan was performed, revealing a bronchopleural fistula in the right hemithorax. The computed tomography scan also revealed a pyo-pneumothorax and lung collapse involving the right middle and lower lobes as well as a thick-walled cavity in the right upper lobe. With the pulmonary complications, particularly the recurrent pneumothorax, bronchopleural fistula, and empyema thoracis, cardiothoracic surgeons were involved, who managed the patient conservatively and maintained the chest tube. The patient continued to be ill with recurrent pneumothorax despite the chest tube, until relatives opted for discharge against medical advice.
CONCLUSIONS: Complicated human immunodeficiency virus-related multidrug-resistant tuberculosis is not uncommon in settings of high human immunodeficiency virus/tuberculosis prevalence and is often associated with significant morbidity and mortality. Early diagnosis and treatment of multidrug-resistant tuberculosis, with rigorous monitoring for human immunodeficiency virus-positive individuals, is necessary to prevent debilitating complications.

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PMCID: PMC9150925
PMID: 35637524 [Indexed for MEDLINE]

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

100. **Cryo-EM structure of Mycobacterium tuberculosis 50S ribosomal subunit bound with clarithromycin reveals dynamic and specific interactions with macrolides.**

Emerg Microbes Infect. 2022 Dec;11(1):293-305. doi: 10.1080/22221751.2021.2022439.

Zhang W(1)(2), Li Z(3)(4), Sun Y(5), Cui P(6), Liang J(7), Xing Q(1), Wu J(6), Xu Y(1), Zhang W(6), Zhang Y(6)(8), He L(1)(9), Gao N(3).

Tuberculosis (TB) is the leading infectious disease caused by Mycobacterium tuberculosis (Mtb). Clarithromycin (CTY), an analog of erythromycin (ERY), is more potent against multidrug-resistance (MDR) TB. ERY and CTY were previously reported to bind to the nascent polypeptide exit tunnel (NPET) near peptidyl

transferase center (PTC), but the only available CTY structure in complex with D. radiodurans (Dra) ribosome could be misinterpreted due to resolution limitation. To date, the mechanism of specificity and efficacy of CTY for Mtb remains elusive since the Mtb ribosome-CTY complex structure is still unknown. Here, we employed new sample preparation methods and solved the Mtb ribosome-CTY complex structure at 3.3Å with cryo-EM technique, where the crucial gate site A2062 (E. coli numbering) is located at the CTY binding site within NPET. Two alternative conformations of A2062, a novel syn-conformation as well as a swayed conformation bound with water molecule at interface, may play a role in coordinating the binding of specific drug molecules. The previously overlooked C-H hydrogen bond (H-bond) and π interaction may collectively contribute to the enhanced binding affinity. Together, our structure data provide a structural basis for the dynamic binding as well as the specificity of CTY and explain of how a single methyl group in CTY improves its potency, which provides new evidence to reveal previously unclear mechanism of translational modulation for future drug design and anti-TB therapy. Furthermore, our sample preparation method may facilitate drug discovery based on the complexes with low water solubility drugs by cryo-EM technique.

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PMCID: PMC8786254
PMID: 34935599 [Indexed for MEDLINE]

Conflict of interest statement: No potential conflict of interest was reported by the author(s).

101. **Computer-aided modeling of triazole analogues, docking studies of the compounds on DNA gyrase enzyme and design of new hypothetical compounds with efficient activities.**

J Biomol Struct Dyn. 2022 Jun;40(9):4004-4020. doi: 10.1080/07391102.2020.1852963. Epub 2020 Dec 15.

Adeniji SE(1), Arthur DE(2), Abdullahi M(1), Abdullahi A(3), Ugbe FA(1).

The increasing problem of multi-drug resistant-tuberculosis has focused attention on developing new drugs that are not only active against drug-resistant tuberculosis, but also shorten the lengthy therapy. Therefore, this work employs the application of modeling technique to predict the inhibition activities of some prominent compounds which been reported to be efficient against Mycobacterium tuberculosis. To accomplish the purpose of this work, multiple regression and genetic function approximation were adopted to create the model. The established model was swayed with topological descriptors; MATS7s, SpMin4_Bhv, TDB3v and RDF70v. More also, interactions between the

compounds and the target protein 'DNA gyrase' were evaluated via molecular docking approach utilizing the PyRx and discovery studio simulation software. Based on the docking analysis, compound 20 has the most noticeable binding affinity of -16.5 kcal/mol. Therefore, compound 20 served as a reference structural template and insight to design fourteen novel hypothetical agents with more prominent anti-tubercular activities. More also, compound 20j was observed with the highest activity among the designed compounds with a prominent binding affinity of -24.3 kcal/mol. Therefore, this research recommends in-vivo, in-vitro screening and pharmacokinetic properties to be carried out in order to determine the toxicity of the designed compounds.Communicated by Ramaswamy H. Sarma.

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PMID: 33317403 [Indexed for MEDLINE]

102. **Is body height a prognostic marker for outcome of tuberculosis treatment?**

Infect Dis (Lond). 2022 Jul;54(7):538-541. doi: 10.1080/23744235.2022.2047777. Epub 2022 Mar 14.

Bach F(1), Wejse C(1)(2)(3), Storgaard M(2)(3), Patsche CB(1)(4).

DOI: 10.1080/23744235.2022.2047777
PMID: 35285382 [Indexed for MEDLINE]

103. **Variants in Bedaquiline-Candidate-Resistance Genes: Prevalence in Bedaquiline-Naive Patients, Effect on MIC, and Association with Mycobacterium tuberculosis Lineage.**

Antimicrob Agents Chemother. 2022 Jun 27:e0032222. doi: 10.1128/aac.00322-22. Online ahead of print.

Rivière E(1)(2), Verboven L(1)(2), Dippenaar A(1), Goossens S(1)(2), De Vos E(1), Streicher E(3), Cuypers B(2)(4), Laukens K(2), Ben-Rached F(5), Rodwell TC(6)(7), Pain A(5)(8), Warren RM(3), Heupink TH(1), Van Rie A(1).

Studies have shown that variants in bedaquiline-resistance genes can occur in isolates from bedaquiline-naive patients. We assessed the prevalence of variants in all bedaquiline-candidate-resistance genes in bedaquiline-naive patients, investigated the association between these variants and lineage, and the effect on phenotype. We used whole-genome sequencing to identify variants in bedaquiline-resistance genes in isolates from 509 bedaquiline treatment naive South African tuberculosis patients. A phylogenetic tree was constructed to investigate the association with the isolate lineage background. Bedaquiline MIC

was determined using the UKMYC6 microtiter assay. Variants were identified in 502 of 509 isolates (98.6%), with the highest (85%) prevalence of variants in the Rv0676c (mmpL5) gene. We identified 36 unique variants, including 19 variants not reported previously. Only four isolates had a bedaquiline MIC equal to or above the epidemiological cut-off value of 0.25 µg/mL. Phylogenetic analysis showed that 14 of the 15 variants observed more than once occurred monophyletically in one Mycobacterium tuberculosis (sub)lineage. The bedaquiline MIC differed between isolates belonging to lineage 2 and 4 (Fisher's exact test, P = 0.0004). The prevalence of variants in bedaquiline-resistance genes in isolates from bedaquiline-naive patients is high, but very few (<2%) isolates were phenotypically resistant. We found an association between variants in bedaquiline resistance genes and Mycobacterium tuberculosis (sub)lineage, resulting in a lineage-dependent difference in bedaquiline phenotype. Future studies should investigate the impact of the presence of variants on bedaquiline-resistance acquisition and treatment outcome.

DOI: 10.1128/aac.00322-22
PMID: 35758754