Literature

1. **Linezolid for Drug-Resistant Tuberculosis.**

2022 Sep 1;387(9):842-843. doi: 10.1056/NEJMe2208554.

Thwaites G(1), Nguyen NV(1).

Comment on
N Engl J Med. 2022 Sep 1;387(9):810-823.

DOI: 10.1056/NEJMe2208554
PMID: 36053511 [Indexed for MEDLINE]

2. **Bedaquiline-Pretomanid-Linezolid Regimens for Drug-Resistant Tuberculosis.**

N Engl J Med. 2022 Sep 1;387(9):810-823. doi: 10.1056/NEJMoa2119430.

Conradie F(1), Bagdasaryan TR(1), Borisov S(1), Howell P(1), Mikiashvili L(1), Ngubane N(1), Samoilova A(1), Skornykova S(1), Tudor E(1), Variava E(1), Yablonskiy P(1), Everitt D(1), Wills GH(1), Sun E(1), Olugbosi M(1), Egizi E(1), Li M(1), Holsta A(1), Timm J(1), Bateson A(1), Crook AM(1), Fabiane SM(1), Hunt R(1), McHugh TD(1), Tweed CD(1), Foraida S(1), Mendel CM(1), Spigelman M(1); ZeNix Trial Team.

Collaborators: Bagdasaryan T, Conradie F, Ngubane N, Howell P, Borisov S, Mikiashvili L, Variava E, Samoilova A, Yablonskiy P, Tudor E, Skornyakov S, Thompson L, Canseco JO, Paleckyte A, Solanki P, Choo L, Witney AA.

Comment in
N Engl J Med. 2022 Sep 1;387(9):842-843.

BACKGROUND: The bedaquiline-pretomanid-linezolid regimen has been reported to have 90% efficacy against highly drug-resistant tuberculosis, but the incidence of adverse events with 1200 mg of linezolid daily has been high. The appropriate dose of linezolid and duration of treatment with this agent to minimize toxic effects while maintaining efficacy against highly drug-resistant tuberculosis are unclear.
METHODS: We enrolled participants with extensively drug-resistant (XDR) tuberculosis (i.e., resistant to rifampin, a fluoroquinolone, and an aminoglycoside), pre-XDR tuberculosis (i.e., resistant to rifampin and to either a fluoroquinolone or an aminoglycoside), or rifampin-resistant tuberculosis that

was not responsive to treatment or for which a second-line regimen had been discontinued because of side effects. We randomly assigned the participants to receive bedaquiline for 26 weeks (200 mg daily for 8 weeks, then 100 mg daily for 18 weeks), pretomanid (200 mg daily for 26 weeks), and daily linezolid at a dose of 1200 mg for 26 weeks or 9 weeks or 600 mg for 26 weeks or 9 weeks. The primary end point in the modified intention-to-treat population was the incidence of an unfavorable outcome, defined as treatment failure or disease relapse (clinical or bacteriologic) at 26 weeks after completion of treatment. Safety was also evaluated.
RESULTS: A total of 181 participants were enrolled, 88% of whom had XDR or pre-XDR tuberculosis. Among participants who received bedaquiline-pretomanid-linezolid with linezolid at a dose of 1200 mg for 26 weeks or 9 weeks or 600 mg for 26 weeks or 9 weeks, 93%, 89%, 91%, and 84%, respectively, had a favorable outcome; peripheral neuropathy occurred in 38%, 24%, 24%, and 13%, respectively; myelosuppression occurred in 22%, 15%, 2%, and 7%, respectively; and the linezolid dose was modified (i.e., interrupted, reduced, or discontinued) in 51%, 30%, 13%, and 13%, respectively. Optic neuropathy developed in 4 participants (9%) who had received linezolid at a dose of 1200 mg for 26 weeks; all the cases resolved. Six of the seven unfavorable microbiologic outcomes through 78 weeks of follow-up occurred in participants assigned to the 9-week linezolid groups.
CONCLUSIONS: A total of 84 to 93% of the participants across all four bedaquiline-pretomanid-linezolid treatment groups had a favorable outcome. The overall risk-benefit ratio favored the group that received the three-drug regimen with linezolid at a dose of 600 mg for 26 weeks, with a lower incidence of adverse events reported and fewer linezolid dose modifications. (Funded by the TB Alliance and others; ZeNix ClinicalTrials.gov number, NCT03086486.).

DOI: 10.1056/NEJMoa2119430
PMID: 36053506 [Indexed for MEDLINE]

3. **Costs of Tuberculosis at 3 Treatment Centers, Canada, 2010-2016.**

Emerg Infect Dis. 2022 Sep;28(9):1814-1823. doi: 10.3201/eid2809.220092.

Campbell JR, Nsengiyumva P, Chiang LY, Jamieson F, Khadawardi H, Mah HK, Oxlade O, Rasberry H, Rea E, Romanowski K, Sabur NF, Sander B, Uppal A, Johnston JC, Schwartzman K, Brode SK.

We estimated costs of managing different forms of tuberculosis (TB) across Canada by conducting a retrospective chart review and cost assessment of

patients treated for TB infection, drug-susceptible TB (DS TB), isoniazid-resistant TB, or multidrug-resistant TB (MDR TB) at 3 treatment centers. We included 90 patients each with TB infection and DS TB, 71 with isoniazid-resistant TB, and 62 with MDR TB. Median per-patient costs for TB infection (in 2020 Canadian dollars) were $804 (interquartile range [IQR] $587-$1,205), for DS TB $12,148 (IQR $4,388-$24,842), for isoniazid-resistant TB $19,319 (IQR $7,117-$41,318), and for MDR TB $119,014 (IQR $80,642-$164,015). Compared with costs for managing DS TB, costs were 11.1 (95% CI 9.1-14.3) times lower for TB infection, 1.7 (95% CI 1.3-2.1) times higher for isoniazid-resistant TB, and 8.1 (95% CI 6.1-10.6) times higher for MDR TB. Broadened TB infection treatment could avert high costs associated with managing TB disease.

DOI: 10.3201/eid2809.220092
PMCID: PMC9423918
PMID: 35997366 [Indexed for MEDLINE]

4. **Factors associated with screening failure and study withdrawal in multidrug-resistant TB.**

Int J Tuberc Lung Dis. 2022 Sep 1;26(9):820-825. doi: 10.5588/ijtld.21.0729.

Schwalb A(1), Cachay R(1), Wright A(2), Phillips PPJ(3), Kaur P(4), Diacon AH(5), Ugarte-Gil C(1), Mitnick CD(6), Sterling TR(2), Gotuzzo E(1), Horsburgh CR(4).

SETTING: Multidrug-resistant TB (MDR-TB) clinical trial in Lima, Peru and Cape Town, South Africa.OBJECTIVE: To identify baseline factors associated with screening failure and study withdrawal in an MDR-TB clinical trial.DESIGN: We screened patients for a randomized, blinded, Phase II trial which assessed culture conversion over the first 6 months of treatment with varying doses of levofloxacin plus an optimized background regimen (ClinicalTrials.gov: NCT01918397). We identified factors for screening failure and study withdrawal using Poisson regression to calculate prevalence ratios and Cox proportional hazard regression to calculate hazard ratios. We adjusted for factors with P < 0.2.RESULTS: Of the 255 patients screened, 144 (56.5%) failed screening. The most common reason for screening failure was an unsuitable resistance profile on sputum-based molecular susceptibility testing (n = 105, 72.9%). No significant baseline predictors of screening failure were identified in the multivariable model. Of the 111 who were enrolled, 33 (30%) failed to complete treatment, mostly for non-adherence and consent withdrawal. No baseline factors predicted study withdrawal in the multivariable model.CONCLUSION: No baseline factors were independently associated with either screening failure or study withdrawal in

this secondary analysis of a MDR-TB clinical trial.

DOI: 10.5588/ijtld.21.0729
PMID: 35996282 [Indexed for MEDLINE]

5. **Revised Definitions of Tuberculosis Resistance and Treatment Outcomes, France, 2006-2019.**

Emerg Infect Dis. 2022 Sep;28(9):1796-1804. doi: 10.3201/eid2809.220458.

Kherabi Y, Fréchet-Jachym M, Rioux C, Yazdanpanah Y, Méchaï F, Pourcher V, Robert J, Guglielmetti L; MDR-TB Management Group.

Collaborators: Aubry A, Bonnet I, Eimer J, Morel F, Veziris N, Cambau E, Lecorché E, Mougari F, Andrejak C, Bourgarit A, Klement E, Rivoire B, Thouvenin G, Tunesi S, Wicky M, Jaspard M, Alauzet C, Escaut L, Ellis-Corbet S, Roux AL.

Definitions of resistance in multidrug-resistant tuberculosis (MDR TB) and extensively drug-resistant tuberculosis (XDR TB) have been updated. Pre-XDR TB, defined as MDR TB with additional resistance to fluoroquinolones, and XDR TB, with additional resistance to bedaquiline or linezolid, are frequently associated with treatment failure and toxicity. We retrospectively determined the effects of pre-XDR/XDR TB resistance on outcomes and safety of MDR TB treatment in France. The study included 298 patients treated for MDR TB at 3 reference centers during 2006-2019. Of those, 205 (68.8%) cases were fluoroquinolone-susceptible MDR TB and 93 (31.2%) were pre-XDR/XDR TB. Compared with fluoroquinolone-susceptible MDR TB, pre-XDR/XDR TB was associated with more cavitary lung lesions and bilateral disease and required longer treatment. Overall, 202 patients (67.8%) had favorable treatment outcomes, with no significant difference between pre-XDR/XDR TB (67.7%) and fluoroquinolone-susceptible MDR TB (67.8%; p = 0.99). Pre-XDR/XDR TB was not associated with higher risk for serious adverse events.

DOI: 10.3201/eid2809.220458
PMCID: PMC9423894
PMID: 35997386 [Indexed for MEDLINE]

6. **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

7. **Pretomanid for tuberculosis treatment: An update for clinical purposes.**

Curr Res Pharmacol Drug Discov. 2022 Sep 9:100128. doi: 10.1016/j.crphar.2022.100128. Online ahead of print.

Occhineri S(1)(2), Matucci T(1)(2), Rindi L(3), Tiseo G(1), Falcone M(1), Riccardi N(1)(4), Besozzi G(4).

Coronavirus disease (COVID-19) pandemic determined a 10 years-set back in tuberculosis (TB) control programs. Recent advances in available therapies may help recover the time lost. While Linezolid (LZD) and Bedaquiline (BDQ), previously Group D second line drugs (SLDs) for TB, have been relocated to Group A, other drugs are currently being studied in regimens for drug resistant TB (DR-TB). Among these, Pretomanid (PA), a recently introduced antimycobacterial drug derived from nitroimidazole with both solid bactericidal and bacteriostatic effect, and with an excellent effectiveness and tolerability profile, is in the spotlight. Following promising data obtained from recently published and ongoing randomized controlled trials (RCTs), the World Health Organization (WHO) determined to include PA in its guidelines for the treatment of rifampicin-resistant (RR), multi drug resistant (MDR) and pre-extensively drug resistant TB (pre-XDR-TB) with BDQ, LZD and Moxifloxacine (MFX) in a 6-month regimen. Although further studies on the subject are needed, PA may also represent a treatment option for drug-susceptible TB (DS-TB), latent TB infection (LTBI) and non tuberculous mycobacteria (NTM). This narrative review aims to examine current implementation options and future possibilities for PA in the never-ending fight against TB.

DOI: 10.1016/j.crphar.2022.100128
PMCID: PMC9461242
PMID: 36105740

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.

8. **Pediatric DR-TB: A Neglected Epidemic.**

Indian J Pediatr. 2022 Sep;89(9):927. doi: 10.1007/s12098-022-04290-1. Epub 2022 Jul 4.

Gupta S(1)(2), Verma AK(3), Kant S(3).

DOI: 10.1007/s12098-022-04290-1
PMID: 35781616 [Indexed for MEDLINE]

9. **Case-control study of vitamin D status and adult multidrug-resistant pulmonary TB.**

Int J Tuberc Lung Dis. 2022 Sep 1;26(9):826-834. doi: 10.5588/ijtld.21.0639.

Shukla A(1), Bromage S(2), Dholakia Y(1), Hemler EC(3), Dev P(1), Govekar L(1), Tipre P(4), Shah D(4), Keshavjee SA(5), Wang M(6), Mistry N(1), Fawzi WW(7).

BACKGROUND: India has the highest prevalence of multidrug-resistant TB (MDR-TB) globally. Vitamin D deficiency is potentially an important risk factor for MDR-TB.METHODS: We conducted a case-control study of 90 newly diagnosed adult MDR-TB cases, 180 household controls and 82 non-household controls in Mumbai, India. Serum 25-hydroxyvitamin D (25(OH)D), anthropometry, clinical status and history, dietary data and sociodemographic data were collected from each participant. Interferon-gamma release assay (IGRA) was also performed in controls to assess latent TB. Multivariable regression was performed to estimate associations between 25(OH)D vs. case status and IGRA positivity.RESULTS: Mean participant age was 33.8 ± 12.0 years; 72.8% had 25(OH)D <20 ng/ml. Mean 25(OH)D was significantly ($P < 0.05$) lower in cases (12.5 ± 7.9) than both household (17.5 ± 11.2) and non-household controls (16.4 ± 9.1). In multivariable models, 25(OH)D concentration was inversely associated with MDR-TB case status among cases and household controls (OR 0.95 per 1 ng/ml, 95% CI 0.92-0.99; $P = 0.015$), and among cases and non-household controls (OR 0.94 per 1 ng/ml, 95% CI 0.89-1.00; $P = 0.033$); 53.6% of controls were IGRA-positive. 25(OH)D status was not associated with IGRA positivity.CONCLUSION: Vitamin D status was independently associated with MDR-TB case status. Research should evaluate the effectiveness of vitamin D supplementation in prevention and adjunctive treatment of MDR-TB.

DOI: 10.5588/ijtld.21.0639
PMID: 35996288 [Indexed for MEDLINE]

10. **Pediatric tuberculosis in India: Justice and human rights.**

Public Health Nurs. 2022 Sep;39(5):1058-1064. doi: 10.1111/phn.13061. Epub 2022 Feb 13.

Mannebach K(1), Dressel A(2), Eason L(2).

Tuberculosis (TB) is the deadliest infectious disease across the world, with the greatest burden occurring in India. Pregnant women and children are especially vulnerable to adverse effects from infection, and they tend to have diminished ability to protect themselves. Malnutrition, HIV, and other causes of immune suppression such as exposure to air pollution make one more prone to serious illness or death from TB infection. Risk factors are influenced by maternal education, access to health care, poverty, nutrition, healthcare stigma, and sanitation, among others. Current literature is heavily clinical, lacking focus on upstream factors, with a skew toward secondary and tertiary prevention strategies (i.e., case finding and treatment), and less emphasis on primary prevention (e.g., wealth equity and environmental regulation). Given concerns with extremely drug resistant TB and because infectious diseases can permeate National borders, public health nurses, and other healthcare professionals must educate themselves and advocate on behalf of vulnerable populations such as children in India. Improved sanitation, air quality monitoring, women's education, and increased access to health care are cost-effective and evidence-based strategies to address pediatric TB in India, a challenge which is grounded in human rights and justice.

DOI: 10.1111/phn.13061
PMID: 35152480 [Indexed for MEDLINE]

11. **Paediatric TB care in the United Kingdom.**

Int J Tuberc Lung Dis. 2022 Sep 1;26(9):814-819. doi: 10.5588/ijtld.21.0581.

Duret A(1), Olgemoeller F(2), Ferreras-Antolin L(3), Whittaker E(4), Cohen JM(5).

BACKGROUND: Care of patients with paediatric TB is delivered in a variety of settings by different clinicians in the United Kingdom. Paediatric practices vary in size. Guidelines on managing children with TB differ in recommendations. These factors contribute to variations in practice.OBJECTIVE: To describe practice among UK professionals caring for children exposed to or infected with TB, and their investigation and treatment.METHODS: From 81 NHS (National Health Service) clinical services, 114 individuals responded to a web-based questionnaire.RESULTS: We describe variation in several areas of practice, with important differences between smaller and larger centres. Most respondents go beyond National Institute for Health & Care Excellence guidance and screen child contacts of extrapulmonary TB. Most respondents would presume pulmonary TB exposed children aged under 2 years to be infected. They would not rely on immunological investigations to rule out infection. There was wide variety in approaches to microbiological diagnosis, and in the use of laboratory investigations to monitor treatment. Many respondents felt unclear on how to manage newborns exposed to TB, or children exposed to multidrug-resistant TB.CONCLUSION: These findings support the case for further developing regional networks providing evidence and consensus-based care for children with TB.

DOI: 10.5588/ijtld.21.0581
PMID: 35996289 [Indexed for MEDLINE]

12. **Evaluation of the MolecuTech(®) REBA MTB-XMDR kit for detection of pre-extensively drug-resistant TB.**

Int J Tuberc Lung Dis. 2022 Sep 1;26(9):869-874. doi: 10.5588/ijtld.21.0606.

Cho EJ(1), Kang MR(2), Kim JH(3), Lee JI(1), Son ES(1), Park CH(4), Aung WW(5), Lee JS(1).

BACKGROUND: Rapid diagnosis of drug-resistant TB is critical for early initiation of effective therapy. YD Diagnostics in South Korea recently developed the MolecuTech® REBA MTB-XMDR test to rapidly detect multidrug-resistant TB (MDR-TB), pre-extensively drug-resistant TB (pre-XDR-TB) and resistance to second-line injectable drugs (SLIDs) simultaneously using a fully automated test platform. This study aimed to evaluate the MolecuTech® test for the detection of MDR- and pre-XDR-TB, as well as SLID resistance.METHODS: A total of 151 clinical Mycobacterium tuberculosis isolates from South Korea were tested using the MolecuTech test, and the results were analysed by comparing these with phenotypic drug susceptibility testing (pDST) and sequencing.RESULTS: Compared to pDST, the MolecuTech test showed a sensitivity and specificity of respectively 97.7% and 100.0% for rifampicin (RIF), 82.4% and 100.0% for isoniazid (INH), 97.5% and 97.2% for fluoroquinolones (FQs), and 94.0% and 98.8%

for SLIDs. Concordances with the sequencing results of each resistance determinant were 99.3% for RIF, 96.7% for INH, 98.7% for FQs and 99.3% for SLIDs.CONCLUSION: The MolecuTech test is an efficient and reliable rapid molecular diagnostic tool for the simultaneous screening of MDR- and pre-XDR-TB.

DOI: 10.5588/ijtld.21.0606
PMID: 35996285 [Indexed for MEDLINE]

13. **Pretomanid development and its clinical roles in treating tuberculosis.**

J Glob Antimicrob Resist. 2022 Sep 7:S2213-7165(22)00216-8. doi: 10.1016/j.jgar.2022.09.001. Online ahead of print.

Fekadu G(1), Tolossa T(2), Turi E(2), Bekele F(3), Fetensa G(4).

Tuberculosis (TB) is the leading infectious cause of mortality worldwide. Despite the development of different anti-tuberculosis drugs, managing resistant Mycobacteria is still challenging. The discovery of novel drugs and new methods of targeted drug delivery have the potential to improve the treatment outcome, lower the duration of treatment, and reduce adverse events. Following bedaquiline and delamanid, pretomanid is the third medicine approved as part of a novel drug regimen for treating drug-resistant TB. It is one of the promising drugs, which has the capacity to shape TB treatment and achieve the End TB strategy set by the World Health Organization. The effectiveness of pretomanid is reported in different observational and clinical studies. But long-term safety data in humans are not yet available and the pretomanid-based regimen is recommended under an operational research framework, which prohibits its wider and programmatic use. We think more study is still needed before pretomanid can be celebrated as a promising candidate treatment for different categories of TB and specific patients. This review covers the update on pretomanid development and its clinical roles in treating Mycobacterium tuberculosis.

DOI: 10.1016/j.jgar.2022.09.001
PMID: 36087906

14. **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]

15. **Hepatocellular Injury in Children Treated for Rifampicin-resistant Tuberculosis: Incidence, Etiology and Outcome.**

Pediatr Infect Dis J. 2022 Sep 6. doi: 10.1097/INF.0000000000003690. Online ahead of print.

Duvenhage J(1), Draper HR(2), Garcia-Prats AJ(2)(3), Winckler J(2), Hesseling AC(2), Schaaf HS(2).

BACKGROUND: Hepatocellular injury has been reported commonly in adults on rifampicin-resistant and multidrug-resistant tuberculosis (RR/MDR-TB) treatment. However, there are limited data in children.
METHODS: Two pharmacokinetic studies of children (0-17 years) routinely treated for RR/MDR-TB were conducted in Cape Town, South Africa between October 2011 and February 2020. Hepatocellular injury adverse events (AEs; defined as elevated alanine aminotransferase [ALT]) were documented serially. Data were analyzed to determine the incidence, etiology, risk factors, management and outcome of ALT elevation.
RESULTS: A total of 217 children, median age 3.6 years (interquartile range, 1.7-7.1 years) at enrollment were included. The median follow-up time was 14.0 months (interquartile range, 9.8-17.2 months). Fifty-five (25.3%) patients

developed an ALT AE. Of these, 43 of 55 (78%) patients had 54 ALT AEs attributed to their RR/MDR-TB treatment. The incidence rate of ALT AEs related to RR-TB treatment was 22.4 per 100 person-years. Positive HIV status and having an elevated ALT at enrollment were associated with time to ALT AE attributed to RR/MDR-TB treatment, with P values 0.0427 and $P < 0.0001$, respectively. Hepatitis A IgM was positive in 11 of 14 (78.6%) severe (grade ≥3) cases of ALT AEs. In 8 of 14 (57%) severe ALT AEs, hepatotoxic drugs were stopped or temporarily interrupted. None had a fatal or unresolved outcome.
CONCLUSIONS: Hepatocellular injury in children on RR/MDR-TB treatment is common, although usually mild; having elevated ALT early in treatment and HIV-positive status are possible risk factors. Hepatitis A was a common etiology of severe ALT AE in children treated for RR/MDR-TB.

DOI: 10.1097/INF.0000000000003690
PMID: 36102699

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

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

Bioorg Chem. 2022 Nov;128:105929. doi: 10.1016/j.bioorg.2022.105929. Epub 2022 Jun 7.

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 [Indexed for MEDLINE]

Conflict of interest statement: Declaration of Competing Interest 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.

17. **Discovery and preclinical evaluations of JBD0131, a novel nitrodihydro-imidazooxazole anti-tuberculosis agent.**

Bioorg Med Chem Lett. 2022 Sep 15;72:128871. doi: 10.1016/j.bmcl.2022.128871. Epub 2022 Jun 28.

Luo W(1), Huang Z(1), Xu D(2), Yang M(2), Zhu Y(2), Shen L(2), Chen S(2), Tao X(3), Bin W(4), Hu Y(1), Franzblau SG(5), Jiang N(6), Wei Y(7), Wei X(8), Ding CZ(9).

Multidrug-resistant pulmonary tuberculosis (MDR-TB) is a major health problem worldwide. The treatment for MDR-TB requires medications for a long duration (up to 20-24 months) with second-line drugs resulting in unfavorable outcomes. Nitroimidazoles are promising antimycobacterial agents known to inhibit both aerobic and anaerobic mycobacterial activity. Delamanid and pretomanid are two nitroimidazoles approved by the regulatory agencies for MDR-TB treatment. However, both agents possess unsatisfactory absorption and QTc prolongation. In our search for a safer nitroimidazole, we discovered JBD0131 (2). It exhibited excellent anti-mycobacterial activity against M. tuberculosis H37Rv in vitro and in vivo, improved PK and absorption, reduced QT prolongation potential of delamanid. JBD0131 is currently in clinical development in China for pulmonary tuberculosis (CTR20202308).

DOI: 10.1016/j.bmcl.2022.128871
PMID: 35777718 [Indexed for MEDLINE]

18. **Assessment of the Carcinogenic Potential of Pretomanid in Transgenic Tg.rasH2 Mice.**

Int J Toxicol. 2022 Sep-Oct;41(5):367-379. doi: 10.1177/10915818221113295. Epub 2022 Jul 18.

Ambroso JL(1), Dillberger J(2), Bruning-Barry R(1), Yang T(3).

Pretomanid is a nitroimidazooxazine antimycobacterial drug that was approved as part of a three-drug oral regimen, consisting of bedaquiline, pretomanid, and linezolid, for 6-months treatment of adults with pulmonary extensively drug-resistant tuberculosis or with complicated forms of multidrug-resistant tuberculosis by the food and drug administration in the United States and regulatory bodies in over 10 other countries. Nitroaromatic compounds as a class carry a risk of genotoxicity and potential carcinogenicity based on reactive metabolite formation. A battery of good laboratory practice genotoxicity studies on pretomanid indicated that the compound was not genotoxic, however its hydroxy imidazole metabolite (M50) was genotoxic in the Ames assay. To assess the in vivo carcinogenic potential of pretomanid, hemizygous Tg.rasH2 mice were administered pretomanid once daily by oral gavage for 26 weeks. Male mice were given pretomanid in vehicle at doses of 0, 5, 15 and 40 mg/kg/day and female mice were given pretomanid in vehicle at doses of 0, 10, 30 and 80 mg/kg/day. Positive control mice of both sexes received intraperitoneal injections of urethane at 1000 mg/kg on Days 1, 3 and 5. There were no pretomanid-related early deaths, tumors, non-neoplastic microscopic findings, or gross necropsy findings at any dose level. The positive control gave the anticipated response of lung tumors. Oral administration of pretomanid to mice produced plasma exposure to the parent compound (high dose AUC of pretomanid 3 times the clinical AUC at the maximum recommended human dose) and exposure to the M50 metabolite (less than 10% of pretomanid) at all dose levels in both sexes. These data show that pretomanid was not carcinogenic in a transgenic mouse model at systemic exposures greater than human therapeutic exposures.

DOI: 10.1177/10915818221113295
PMCID: PMC9411704
PMID: 35849539 [Indexed for MEDLINE]

Conflict of interest statement: Declaration of conflicting interests: The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Tian Yang is an employee of the TB Alliance (The Global Alliance for TB Drug Development), a non-profit organization dedicated to the discovery and development of improved TB therapeutics. The TB Alliance is funded by governments and foundations, through which this research was supported. Jeffrey Ambroso and Rebecca Bruning-Barry are employees of RTI International, an independent, non-profit scientific research and development institute, and consult on TB Alliance projects. John Dillberger is an independent consultant on TB Alliance projects.

19. **Synthesis and evaluation of inhibitors of Mycobacterium tuberculosis UGM using bioisosteric replacement.**

Bioorg Med Chem. 2022 Sep 1;69:116896. doi: 10.1016/j.bmc.2022.116896. Epub 2022 Jun 23.

Fu J(1), He Z(2), Fu H(3), Xia Y(2), N'Go I(4), Lou H(5), Wu J(2), Pan W(6), Vincent SP(7).

There is a dearth of tuberculosis (TB) drug development activity as current therapeutic treatments are inadequate due to the appearance of drug-resistant TB. The enzyme UDP-galactopyranose mutase (UGM) is involved in the biosynthesis of galactan which is essential for cell wall integrity and bacterial viability. Its inhibition has thus been featured as profitable strategy for anti-TB drug discovery. In this study, we report on the synthesis of amides derived from rosmarinic acid, their inhibitory effect towards purified UGM using three distinct biochemical assays: FP, HPLC and SPR. The rosmarinic amides generally showed a significantly higher affinity for UGM than the corresponding rosmarinic ester. In particular, compound 5h displayed interesting binding affinity values (Kd = 58 ± 7, 63 ± 9 μM towards KpUGM and MtUGM respectively). Furthermore, a new UGM SPR assay was established and confirmed that 5h binds to UGM with a dissociation constant of 104.8 ± 6.5 μM. Collectively, this study validates the amide bioisosteric strategy which has been successfully implemented to develop UGM inhibitors from rosmarinic acid, providing a substantial basis for further design of novel UGM inhibitors and anti-mycobacterial agents.

DOI: 10.1016/j.bmc.2022.116896
PMID: 35777270 [Indexed for MEDLINE]

20. **When is the use of suboptimal treatment in functionally untreatable multi-drug resistant tuberculosis morally permissible?**

Glob Public Health. 2022 Sep 18:1-10. doi: 10.1080/17441692.2022.2120047. Online ahead of print.

Arora C(1).

Multidrug-resistant tuberculosis (MDR-TB) is well recognised as a serious threat to controlling and ending the TB epidemic. Treatment is time-intensive and

costly. Current treatment guidelines recommend the use of at least four effective drugs plus pyrazinamide for a period of 18-24 months. There are, however, situations in which this is not feasible. This may be due to severe patterns of drug-resistance, poor tolerance to the medications, or supply chain issues. In this paper, I use the term functionally untreatable MDR-TB to refer to such situations. Patients may be assigned to waiting lists until appropriate medications are available, and many die while awaiting treatment. Clinicians face a serious ethical dilemma in these cases, and some may choose to treat their patients with suboptimal regimens in the interim. While this practice may alleviate symptoms and even cure some patients, it is known to extend drug-resistance, limiting further the availability of efficacious anti-TB medicines. This paper explores the relevant ethical considerations faced by clinicians providing MDR-TB treatment, and how this differs from formal ethical principles and guidance. It outlines extreme situations in which suboptimal regimens may be considered, and requisite conditions to be fulfilled by stakeholders for this to be morally permissible.

DOI: 10.1080/17441692.2022.2120047
PMID: 36121019

21. **Design, synthesis and biological evaluation of (Quinazoline 4-yloxy)acetamide and (4-oxoquinazoline-3(4H)-yl)acetamide derivatives as inhibitors of Mycobacterium tuberculosis bd oxidase.**

Eur J Med Chem. 2022 Nov 15;242:114639. doi: 10.1016/j.ejmech.2022.114639. Epub 2022 Aug 6.

Kumar A(1), Kumari N(2), Bhattacherjee S(1), Venugopal U(2), Parwez S(3), Siddiqi MI(3), Krishnan MY(4), Panda G(5).

New chemical scaffolds with novel mechanism of action are urgently needed for the treatment of drug resistant tuberculosis. The oxidative phosphorylation pathway of Mycobacterium tuberculosis consists of multiple clinically validated drug targets. This pathway can function through any one of the two terminal oxidases-the proton pumping cytochrome bc1-aa3 supercomplex, or the less energy efficient but high affinity cytochrome bd oxidase. Inhibiting the bc1 complex alone has been found bacteriostatic and not bactericidal. On the other hand, inhibition of both these oxidases turns lethal to the pathogen. In the present study, we used a bc1 complex mutant of M. tuberculosis to screen (Quinazoline 4-yloxy)acetamide and (4-oxoquinazoline-3(4H)-yl)acetamide derivatives against the alternate oxidase, i.e., cytochrome bd oxidase. Two molecules, S-021-0601 and S-021-0607 were found to inhibit the mutant with MICs 8 and 16 μM respectively, compared to MICs of 128 and 256 μM against the wild type M.

tuberculosis. In the wild type, one of the compounds showed synergism with Q203, an inhibitor of bc1 complex, in inhibiting growth under aerobic conditions. Both compounds showed synergism with Q203 in depleting bacterial ATP and inhibiting oxygen consumption. Both the compounds at 32 μM (one-fourth or one-eighth of their MICs for wild type) were bactericidal to wild type bacteria under hypoxic condition, causing ∼1.9 log10 reduction in viable counts which increased to ∼4-log10 when combined with Q203.

DOI: 10.1016/j.ejmech.2022.114639
PMID: 35973312

Conflict of interest statement: Declaration of competing interest 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.

22. **Major revision version 11.0 of the European AIDS Clinical Society Guidelines 2021.**

HIV Med. 2022 Sep;23(8):849-858. doi: 10.1111/hiv.13268. Epub 2022 Mar 25.

Ryom L(1)(2), De Miguel R(3), Cotter AG(4)(5), Podlekareva D(1)(6), Beguelin C(7), Waalewijn H(8), Arribas JR(3), Mallon PWG(4)(5), Marzolini C(9)(10), Kirk O(1)(11), Bamford A(12), Rauch A(7), Molina JM(13), Kowalska JD(14), Guaraldi G(15), Winston A(16), Boesecke C(17), Cinque P(18), Welch S(19), Collins S(20), Behrens GMN(21)(22); EACS Governing Board.

BACKGROUND: The European AIDS Clinical Society (EACS) Guidelines were revised in 2021 for the 17th time with updates on all aspects of HIV care.
KEY POINTS OF THE GUIDELINES UPDATE: Version 11.0 of the Guidelines recommend six first-line treatment options for antiretroviral treatment (ART)-naïve adults: tenofovir-based backbone plus an unboosted integrase inhibitor or plus doravirine; abacavir/lamivudine plus dolutegravir; or dual therapy with lamivudine or emtricitabine plus dolutegravir. Recommendations on preferred and alternative first-line combinations from birth to adolescence were included in the new paediatric section made with Penta. Long-acting cabotegravir plus rilpivirine was included as a switch option and, along with fostemsavir, was added to all drug-drug interaction (DDI) tables. Four new DDI tables for anti-tuberculosis drugs, anxiolytics, hormone replacement therapy and COVID-19 therapies were introduced, as well as guidance on screening and management of anxiety disorders, transgender health, sexual health for women and menopause.

The sections on frailty, obesity and cancer were expanded, and recommendations for the management of people with diabetes and cardiovascular disease risk were revised extensively. Treatment of recently acquired hepatitis C is recommended with ongoing risk behaviour to reduce transmission. Bulevirtide was included as a treatment option for the hepatitis Delta virus. Drug-resistant tuberculosis guidance was adjusted in accordance with the 2020 World Health Organization recommendations. Finally, there is new guidance on COVID-19 management with a focus on continuance of HIV care.
CONCLUSIONS: In 2021, the EACS Guidelines were updated extensively and broadened to include new sections. The recommendations are available as a free app, in interactive web format and as an online pdf.

DOI: 10.1111/hiv.13268
PMID: 35338549 [Indexed for MEDLINE]

23. **Recognition of multi-drug resistant cutaneous tuberculosis and the need for empirical therapy.**

Int J Dermatol. 2022 Oct;61(10):1294-1297. doi: 10.1111/ijd.16292. Epub 2022 May 22.

Ramesh V(1), Mahajan R(2), Sen MK(3).

DOI: 10.1111/ijd.16292
PMID: 35599298 [Indexed for MEDLINE]

24. **Recognition of specific immunogenic antigens with potential diagnostic value in multi-drug resistant Mycobacterium tuberculosis inducing humoral immunity in MDR-TB patients.**

Infect Genet Evol. 2022 Sep;103:105328. doi: 10.1016/j.meegid.2022.105328. Epub 2022 Jul 3.

Hadizadeh Tasbiti A(1), Badmasti F(2), Siadat SD(1), Fateh A(1), Yari F(3), GHzanfari Jajin M(4), Yari S(5).

Tuberculosis (TB) as a public health crisis is caused by the intracellular bacterium Mycobacterium tuberculosis. Detection of immunogenic proteins in TB is valuable for the development of diagnostic tests, vaccine formulations and

monitoring treatment outcome. In this study, we differentiated the immune-reactivity of proteins in multidrug-resistant tuberculosis (MDRTB) and drug-susceptible strains using purified anti-MDRTB antibodies isolated from inpatients. Our data showed that the anti- MDRTB antibody was well able to detect the MDR strain in the patient's sputum. The immunogenic proteins of MDRTB were purified by affinity chromatography and subjected to matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectrometry. Analysis of the data revealed that seven MDRTB immunogenic proteins, including Rv2986c (HupB), Rv3699, Rv1133c (MetE), Rv0440 (GroEL), Rv3057c, Rv2558 and Rv2971 are involved in DNA stability, metabolism, cellular processes and some unknown functions. Similarities in the electrophoresis protein profiles were evident between the extracts of MDR and sensitive TB strains. However, the protein expression patterns of MDRTB isolates were distinguishable from that formed by susceptible TB strains.

DOI: 10.1016/j.meegid.2022.105328
PMID: 35788051 [Indexed for MEDLINE]

25. **Adjunctive Zoledronate + IL-2 administrations enhance anti-tuberculosis Vγ2Vδ2 T-effector populations, and improve treatment outcome of multidrug-resistant tuberculosis(1).**

Emerg Microbes Infect. 2022 Dec;11(1):1790-1805. doi: 10.1080/22221751.2022.2095930.

Shen H(1), Yang E(1)(2), Guo M(3), Yang R(1), Huang G(1), Peng Y(1), Sha W(1), Wang F(4), Shen L(2).

Multidrug-resistant tuberculosis (MDR-TB) is a refractory disease with high mortality rate due to no or few choices of antibiotics. Adjunctive immunotherapy may help improve treatment outcome of MDR-TB. Our decade-long studies demonstrated that phosphoantigen-specific Vγ2Vδ2 T cells play protective roles in immunity against TB. Here, we hypothesized that enhancing protective Vγ2Vδ2 T-effector cells could improve treatment outcome of MDR-TB. To address this, we employed clinically approved drugs Zoledronate (ZOL) and IL-2 to induce anti-TB Vγ2Vδ2 T-effector cells as adjunctive immunotherapy against MDR-TB infection of macaques. We found that adjunctive ZOL/IL-2 administrations during TB drugs treatment of MDR-TB-infected macaques significantly expanded Vγ2Vδ2 T cells and enhanced/sustained Vγ2Vδ2 T-effector subpopulation producing anti-TB cytokines until week 21. ZOL/IL-2 administrations, while expanding Vγ2Vδ2 T cells, significantly increased/sustained numbers of circulating CD4+ Th1 and CD8+

Th1-like effector populations, with some γδ T- or αβ T-effector populations trafficking to airway at week 3 until week 19 or 21 after MDR-TB infection. Adjunctive ZOL/IL-2 administrations after MDR-TB infection led to lower bacterial burdens in lungs than TB drugs alone, IL-2 alone or saline controls, and resulted in milder MDR-TB pathology/lesions. Thus, adjunctive Zoledronate + IL-2 administrations can enhance anti-TB Vγ2Vδ2 T- and αβ T-effector populations, and improve treatment outcome of MDR-TB.

DOI: 10.1080/22221751.2022.2095930
PMCID: PMC9310823
PMID: 35765887 [Indexed for MEDLINE]

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

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

J Glob Antimicrob Resist. 2022 Sep;30:302-307. doi: 10.1016/j.jgar.2022.06.009. Epub 2022 Jun 15.

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 East African-Indian (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 profiles.
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) previously not detected by conventional drug-susceptibility testing.
CONCLUSION: 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 the association between lineage and drug-resistant TB in Malaysia is scarce, and more studies are needed to determine the significance of such association, if any, in our local settings.

DOI: 10.1016/j.jgar.2022.06.009
PMID: 35717019 [Indexed for MEDLINE]

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

27. **High clustering rate and genotypic drug-susceptibility screening for the newly recommended anti-tuberculosis drugs among global extensively drug-resistant Mycobacterium tuberculosis isolates.**

Emerg Microbes Infect. 2022 Dec;11(1):1857-1866. doi: 10.1080/22221751.2022.2099304.

Trisakul K(1)(2), Nonghanphithak D(1)(2), Chaiyachat P(1)(2), Kaewprasert O(1)(2), Sakmongkoljit K(3), Reechaipichitkul W(1)(2), Chaiprasert A(4), Blair D(5), Clark TG(6), Faksri K(1)(2).

Multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) make TB difficult to control. Global susceptibility data for six newly recommended anti-TB drugs against M/XDR-TB are still limited. Using publicly available whole-genome sequences, we determined the proportion of 513 phenotypically XDR-TB isolates that carried mutations associated with resistance against these drugs (bedaquiline, clofazimine, linezolid, delamanid, pretomanid and cycloserine). Mutations of Rv0678 and Rv1979c were detected in 69/513 isolates (13.5%) for bedaquiline resistance and 79/513 isolates (15.4%) for clofazimine resistance with additional mmpL5 mutations. Mutations conferring resistance to delamanid were detected in fbiB and ddn genes for 11/513 isolates (2.1%). For pretomanid, a mutation was detected in the ddn gene for 3/513 isolates (0.6%). Nineteen mutations of pykA, cycA, ald, and alr genes, conferring resistance to cycloserine, were found in 153/513 isolates (29.8%). No known mutations associated with linezolid resistance were detected. Cluster analysis showed that 408/513 isolates fell within 99 clusters and that 354 of these isolates were possible primary drug-resistant TB (292 XDR-TB, 57 pre-XDR-TB and 5 MDR-TB). Clonal transmission of primary XDR isolates might contribute significantly to the high prevalence of DR-TB globally.

DOI: 10.1080/22221751.2022.2099304
PMCID: PMC9336503
PMID: 35792049 [Indexed for MEDLINE]

Conflict of interest statement: No potential conflict of interest was reported

by the author(s).

28. **Population Pharmacokinetic Modeling of Bedaquiline among Multidrug-Resistant Pulmonary Tuberculosis Patients from China.**

Antimicrob Agents Chemother. 2022 Sep 15:e0081122. doi: 10.1128/aac.00811-22. Online ahead of print.

Zou J(#)(1), Chen S(#)(2)(3), Rao W(4), Fu L(5), Zhang J(1), Liao Y(4), Zhang Y(1), Lv N(1), Deng G(5), Yang S(1), Lin L(4), Li L(6), Liu S(4), Qu J(1).

Bedaquiline has been widely used as a part of combination dosage regimens for the treatment of multidrug-resistant tuberculosis (MDR-TB) patients with limited options. Although the effectiveness and safety of bedaquiline have been demonstrated in clinical trials, limited studies have investigated the significant pharmacokinetics and the impact of genotype on bedaquiline disposition. Here, we developed a population pharmacokinetic model of bedaquiline to describe the concentration-time data from Chinese adult patients diagnosed with MDR-TB. A total of 246 observations were collected from 99 subjects receiving the standard recommended dosage. Bedaquiline disposition was well described by a one-compartment model with first-order absorption. Covariate modeling identified that gamma-glutamyl transferase (GGT) and the single-nucleotide polymorphism (SNP) rs319952 in the AGBL4 gene were significantly associated with the apparent clearance of bedaquiline. The clearance (CL/F) was found to be 1.4 L/h lower for subjects with allele GG in SNP rs319952 than for subjects with alleles AG and AA and to decrease by 30% with a doubling in GGT. The model-based simulations were designed to assess the impact of GGT/SNP rs319952 on bedaquiline exposure and showed that patients with genotype GG in SNP rs319952 and GGT ranging from 10 to 50 U/L achieved the targeted maximum serum concentration at steady state (Cmax,ss). However, when GGT was increased to 100 U/L, Cmax,ss was 1.68-fold higher than the highest concentration pursued. The model developed provides the consideration of genetic polymorphism and hepatic function for bedaquiline dosage in MDR-TB adult patients.

DOI: 10.1128/aac.00811-22
PMID: 36106884

29. **Correlation of serum amyloid A1 and interleukin-1beta in response to anti-tubercular therapy.**

Am J Med Sci. 2022 Sep;364(3):316-326. doi: 10.1016/j.amjms.2021.12.014. Epub

2022 Apr 20.

Mishra P(1), Verma VK(1), Barman L(1), Sharma J(1), Gupta P(1), Mohan A(2), Arya DS(3).

BACKGROUND: Host biomarkers are needed to monitor the response to anti-tubercular therapy (ATT) for ensuring effective therapy and preventing drug-resistant tuberculosis. We sought to find the correlation between the serum levels of SAA1 and IL-1beta in response to ATT in adult patients with pulmonary TB (PTB) or extra-pulmonary TB (EPTB).
METHODS: Blood samples of 32 patients with PTB and 28 patients with EPTB were analyzed. The blood samples were collected at baseline, two months and six months following treatment initiation. SAA1 and IL-1beta levels were measured by enzyme linked immunosorbent assay (ELISA).
RESULTS: In the PTB group, the mean levels of SAA1 decreased significantly ($p < 0.001$) after the intensive phase (two months) and continuous phase (six months) of ATT in comparison with the baseline value. IL-1beta values also decreased significantly ($p = 0.005$) after the intensive phase (two months) compared with the baseline values. In the EPTB group, there was a significant reduction in the mean serum level of SAA1 ($p < 0.001$) and IL-1beta ($p = 0.001$) after the intensive phase (two months) in comparison with the baseline value, whereas the reduction at six months was not significant.
CONCLUSIONS: SAA1 and IL-1beta may be useful potential treatment-monitoring biomarkers, especially in the intensive phase of therapy for both PTB and EPTB.

DOI: 10.1016/j.amjms.2021.12.014
PMID: 35452629 [Indexed for MEDLINE]

Conflict of interest statement: Declaration of Competing Interest The authors declare that they have no conflict of interest.

30. **Re-evaluating the merits of decentralization as a core strategy for effective delivery of drug-resistant tuberculosis care in Pakistan.**

Health Policy Plan. 2022 Sep 13;37(8):979-989. doi: 10.1093/heapol/czac038.

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

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

DOI: 10.1093/heapol/czac038
PMCID: PMC9384034
PMID: 35527232 [Indexed for MEDLINE]

31. **Whole-Genome Sequencing and Epidemiological Investigation of Tuberculosis Outbreaks in High Schools in Hunan, China.**

Infect Drug Resist. 2022 Sep 2;15:5149-5160. doi: 10.2147/IDR.S371772. eCollection 2022.

Xu Z(#)(1)(2), Liu H(#)(3), Liu Y(#)(4), Tang Y(2), Tan Y(2), Hu P(2), Zhang C(2), Yang C(4), Wan K(3), Wang Q(2).

BACKGROUND: Tuberculosis (TB) seriously threatens individual and public health. Recently, TB outbreaks in schools have been reported more frequently in China and have attracted widespread attention. We reported three TB outbreaks in high schools in Hunan Province, China.
METHODS: When a tuberculosis patient was reported in a school, we carried out field epidemiological investigations, including tuberculin skin testing (TST), chest X-ray (CXR) and laboratory test for all close contacts, and whole-genome

sequencing (WGS) analyses to understand the transmission patterns, the causes and the risk factors for the outbreaks, thereby providing a foundation for the control of TB epidemics in schools.
RESULTS: A total of 49 students with TB patients were identified in the three schools where TB outbreaks occurred, including nine patients in School A, 14 patients in School B, and 26 patients in School C. In Schools A, B and C, the putative attack rates in the classes of the index case were 13.8% (8/58), 7.6% (5/66), and 40.4% (21/52), while the putative attack rates of expanding screening in the school were 0.3% (1/361), 0.2% (9/3955), and 0.2% (5/2080), respectively. Thirteen patients had patient delay, with a median delay interval of 69 days (IQR 30.5-113 days). Twelve patients had a healthcare diagnostic delay with a median delay interval of 32 days (IQR 24-82 days). Phylogenetic analysis of culture-positive patients revealed that most of them shared a small genetic distance (≤12 SNPs), with three separate genetic clusters (including one MDR-TB genomic cluster), indicating the recent transmission of Mycobacterium tuberculosis strains.
CONCLUSION: This combination of field investigation and WGS analysis revealed the transmission of three TB outbreaks in schools. Reinforced implementation is needed to improve timely case finding and reduce diagnosis delay in routine TB control in the school population.

DOI: 10.2147/IDR.S371772
PMCID: PMC9448353
PMID: 36082241

Conflict of interest statement: The authors declare that there are no conflicts of interest.

32. **The Correlations of Minimal Inhibitory Concentration Values of Anti-TB Drugs with Treatment Outcomes and Clinical Profiles in Patients with Multidrug-Resistant Tuberculosis (MDR-TB) in China.**

Infect Drug Resist. 2022 Sep 7;15:5275-5287. doi: 10.2147/IDR.S374687. eCollection 2022.

Tang Q(1), Ke H(1), Sun WW(1), Zhang SJ(1), Fan L(1).

OBJECTIVE: It is a challenge to obtain satisfactory treatment outcomes for patients with multidrug-resistant/rifampicin-resistant tuberculosis (MDR/RR-TB); the study aims to correlate the Minimum Inhibitory Concentration (MIC) value of drugs with the outcome of patients with MDR/RR-TB to obtain an understanding for

better regimens and optimal outcomes.
METHODS: The patients diagnosed with MDR/RR-TB were retrospectively enrolled from January 1, 2018 to December 31, 2019, recorded clinical characteristics, MIC DST (Drug Susceptibility Test) results, and followed the treatment outcome. The data were analyzed on the correlations of MIC DST values with outcomes and clinical characteristics.
RESULTS: A total of 276 patients with MDR/RR-TB were included, containing 98 cases (35.5%) with newly treated patients and 178 cases (64.5%) with re-treated patients. A total of 220 cases recorded treatment success (79.7%) and 49 cases recorded treatment failure or died. MIC values of isoniazid (H), moxifloxacin (Mfx), and ethionamide (Eto) in newly treated patients were lower than those in retreated patients, and resistance levels of Mfx and H were closely associated with the treatment outcome ($P < 0.05$) while those of other drugs had no close association with treatment outcome.
CONCLUSIONS: MIC values of some anti-TB drugs, such as fluoroquinolones (FQs) and H, can reflect the treatment outcome for patients with MDR/RR-TB, which can contribute to making regimens for better treatment outcomes.

DOI: 10.2147/IDR.S374687
PMCID: PMC9464630
PMID: 36106053

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

33. **Clinical Manifestation, Imaging Features and Treatment Follow-up of 29 Cases with Hepatic Tubercolosis.**

Mediterr J Hematol Infect Dis. 2022 Sep 1;14(1):e2022063. doi: 10.4084/MJHID.2022.063. eCollection 2022.

Liu S(1), Chen W(2), Shi J(1), Ye X(1), Ning H(1), Pan N(1), Jiang X(1).

To understand the clinical and imaging manifestations and the treatment and follow-up of hepatic tuberculosis (HTB), we retrospectively analysed the clinical and imaging data of 29 patients with HTB who had been diagnosed clinically or by biopsy, and the clinical and imaging data had been summarised. Patient characteristics were followed up after anti-TB drug treatment. The median age of the 29 patients with HTB was 37 years, and most were male (58.6%). The patient's symptoms included fever (48.2%), respiratory symptoms (27.5%), abdominal pain (24.1%), and abdominal distension (10.3%). Elevated erythrocyte

sedimentation rate (79.3%), elevated serum C-reactive protein (75.8%) and hypoalbuminemia (62.0%) were common features. Three patients were serologically positive for acquired human immunodeficiency syndrome, and two were serologically positive for hepatitis B surface antigen with normal tumour markers. The 29 patients with HTB included 17 with serous HTB, 9 with parenchymal HTB (8 with parenchymal nodular HTB and 1 with parenchymal miliary HTB), 1 with intrahepatic abscess type HTB, and 2 with hilar HTB. Approximately 86% of the patients also had pulmonary TB. Most of the serous HTB patients also had tuberculous peritonitis. Enhanced computerized tomography scans of the serous and parenchymal HTB cases showed the progressive development of lesions. Abnormal blood perfusion was observed in the hepatic artery, and the clearest evidence of TB was observed in the hepatic portal vein. Magnetic resonance imaging indicated that the lesions returned a high signal in the diffusion-weighted imaging sequence. However, the lesions' apparent diffusion coefficient values reflected high signals. The Xpert MTB/RIF test detected Mycobacterium TB complex in the liver biopsy fluid from 10 patients. Regarding histopathology, one patient showed granulomatous inflammation, and one patient's acid-fast bacillus (AFB) stain was positive. The treatment of two patients was stopped due to their adverse reactions to the drugs and the risk of creating drug-resistant TB. The remaining patients received anti-TB treatment, but one subsequently died, and two were unavailable for follow-up. The clinical symptoms of HTB are difficult to detect, and it has diverse manifestations by imaging, with no obvious specificity in terms of pathological results. Therefore, follow-up of liver lesions for checking anti-TB therapy is another method for diagnosing HTB. In addition, early active anti-TB treatment can achieve good curative results.

DOI: 10.4084/MJHID.2022.063
PMCID: PMC9448267
PMID: 36119453

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

34. **Development and Validation of a Nomogram for Prediction of QT Interval Prolongation in Patients Administered Bedaquiline-Containing Regimens in China: a Modeling Study.**

Antimicrob Agents Chemother. 2022 Sep 1:e0203321. doi: 10.1128/aac.02033-21. Online ahead of print.

Liu F(#)(1)(2), Gao J(#)(1), Gao M(#)(3), Liu Y(#)(1), Shu W(1), Xie L(3), Sun Y(1), Zhang L(1), Li L(1), Pang Y(4).

Corrected QT duration (QTc) interval prolongation is the most frequent adverse event associated with bedaquiline (BDQ) use. It may affect the safety of antituberculosis therapy, which leads to the consequent demands of needing to monitor during therapy. Our objective was to establish and validate a prediction model for estimating the risk of QTc prolongation after initiation of BDQ-containing regimens to multidrug-resistant tuberculosis (MDR-TB) patients. We constructed an individualized nomogram model based on baseline demographic and clinical characteristics of each patient within a Chinese cohort during BDQ treatment. The generalizability of this model was further validated through use of externally acquired data obtained from Beijing Chest Hospital from 2019 to 2020. Overall, 1,215 and 165 patients were included in training and external validation cohorts, respectively, whereby during anti-TB drug treatment, QTc prolongation was observed in 273 (22.5%) and 29 (17.6%) patients within these respective cohorts, for whom QTc values were >500 ms in 86 (31.5%) and 10 (34.7%) patients, respectively. Next, a total of four Cox proportional hazards models were created and assessed; then, nomograms derived from the models were plotted based on independent predictors of clofazimine, baseline QTc interval, creatinine, extensive drug-resistance (XDR), moxifloxacin, levofloxacin, and sex. Nomogram analysis revealed concordance index values of 0.723 (95% confidence interval [CI], 0.695 to 0.750) for the training cohort and 0.710 (95% CI, 0.627 to 0.821) for the external validation cohort, thus indicating relatively fair agreement between predicted and observed probabilities of QTc prolongation occurrence based on data obtained during 8-week, 16-week, and 24-week anti-TB treatment of both cohorts. Taken together, results obtained using these models demonstrated that coadministration of clofazimine and abnormal baseline QTc interval significantly contributed to QTc prolongation development during MDR-TB patient treatment with a BDQ-containing anti-TB treatment regimen.

DOI: 10.1128/aac.02033-21
PMID: 36047781

35. **A retrospective cohort study on the treatment outcomes and genotyping of isoniazid-resistant tuberculosis patients in Eastern China.**

J Glob Antimicrob Resist. 2022 Sep;30:335-339. doi: 10.1016/j.jgar.2022.07.003. Epub 2022 Jul 8.

Li Y(1), Shi J(2), Song W(3), Shao Y(4), Zhu L(4), Chen C(5).

OBJECTIVES: Isoniazid resistance might be overlooked because of the priority of detection of rifampicin-resistant tuberculosis. It was urgent to reveal the

current situation of isoniazid-resistant tuberculosis (HR-TB), including unfavorable outcomes and bacterial factors.
METHODS: A retrospective cohort study was undertaken including 120 patients with HR-TB and 193 patients with drug-sensitive tuberculosis (DS-TB). 24-loci MIRU-VNTR and Spoligotyping were adopted for genotyping.
RESULTS: We found 106 cases (88.3%) of HR-TB and 165 cases (85.5%) of DS-TB were treated with the first-line drugs. Meanwhile, 12 (10.0%) patients of the HR-TB group and 7 (3.63%) patients of the DS-TB group involved adverse treatment outcomes ($\chi 2 = 5.271$, $P = 0.028$). Seventy-eight DNA from HR Mycobacterium tuberculosis and 114 DNA from DS M. tuberculosis were available for MIRU-VNTR and Spoligotyping. The clustering rate was 17.9% (14/78) for HR-TB and 16.7% (19/114) for DS-TB, and reached no significant difference ($\chi 2 = 0.05$, $P = 0.8171$). The Beijing family strains accounted for 83.7% (65/78) of HR-TB and 80.0% (91/114) of DS-TB ($\chi 2 = 0.37$, $P = 0.5407$). The adverse treatment outcomes for HR-TB all occurred in patients infected with Beijing family strains (13.8%), but no difference was found between Beijing and non-Beijing genotypes ($P = 0.342$).
CONCLUSION: Adverse outcomes were significantly more frequent in patients with HR-TB than in those with DS-TB, and most of the patients with HR-TB were receiving a standard first-line regimen. Although the clustering rate and Beijing genotype distribution amongst HR-TB and DS-TB showed no significant difference, the Beijing genotype was the dominant genotype and its proportion was slightly higher amongst HR-TB than amongst DS-TB.

DOI: 10.1016/j.jgar.2022.07.003
PMID: 35817264 [Indexed for MEDLINE]

36. **High proportion of tuberculosis transmission among social contacts in rural China: a 12-year prospective population-based genomic epidemiological study.**

Emerg Microbes Infect. 2022 Dec;11(1):2102-2111. doi: 10.1080/22221751.2022.2112912.

Li M(1)(2), Guo M(3), Peng Y(4), Jiang Q(1)(5), Xia L(6), Zhong S(7), Qiu Y(3), Su X(7), Zhang S(6), Yang C(1)(8), Mijiti P(1), Mao Q(1), Takiff H(9), Li F(4), Chen C(6), Gao Q(1)(2).

ABSTRACTTuberculosis (TB) is more prevalent in rural than urban areas in China, and delineating TB transmission patterns in rural populations could improve TB control. We conducted a prospective population-based study of culture-positive pulmonary TB patients diagnosed between July 1, 2009 and December 31, 2020 in

two rural counties in China. Genomic clusters were defined with a threshold distance of 12-single-nucleotide-polymorphisms, based on whole-genome sequencing. Risk factors for clustering were identified by logistic regression. Transmission links were sought through epidemiological investigation of genomic-clustered patients. Of 1517 and 751 culture-positive pulmonary TB patients in Wusheng and Wuchang counties, respectively, 1289 and 699 strains were sequenced. Overall, 624 (31.4%, 624/1988) patients were grouped into 225 genomic clusters. Epidemiological links were confirmed in 41.8% (196/469) of clustered isolates, including family (32.7%, 64/196) and social contacts (67.3%, 132/196). Social contacts were generally with relatives, within the community or in shared aggregated settings outside the community, but the proportion of clustered contacts in each category differed between the two sites. The time interval between diagnosis of student cases and contacts was significantly shorter than family and social contacts, probably due to enhanced student contact screening. Transmission of multidrug-resistant (MDR) strains was likely responsible for 81.4% (83/102) of MDR-TB cases, with minimal acquisition of additional resistance mutations. A large proportion of TB transmission in rural China occurred among social contacts, suggesting that active screening and aggressive contact tracing could benefit TB control, but contact screening should be tailored to local patterns of social interactions.

DOI: 10.1080/22221751.2022.2112912
PMCID: PMC9448380
PMID: 35950916 [Indexed for MEDLINE]

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

37. **Separation and Characterization of Novel Degradation and Process Related Impurities of Bedaquiline Bulk Drug.**

J Chromatogr Sci. 2022 Sep 3;60(7):678-691. doi: 10.1093/chromsci/bmab117.

Vanavi PJ(1), Rajput SJ(1).

Bedaquiline (BDQ) is a new drug approved by United States Food and Drug Administration (USFDA) in 2012 for the treatment of drug-resistant tuberculosis, which has become a major threat globally. The manuscript presents the development of three liquid chromatography (LC) based analytical methods. The first is a stability indicating RP-HPLC (reverse phase-high performance liquid chromatography) method to analyze the BDQ in presence of its degradation products. Another UPLC/ESI-MS (ultra-performance liquid chromatography/electron spray ionization-mass spectrometry) method was developed for the identification

of different degradation based and process related impurities and the third, preparative HPLC method was developed for the isolation of major degradation products. Eleven degradation products and one process related impurity were identified using UPLC/ESI-MS whereas preparative HPLC was used to isolate two degradation products and their chemical structure was elucidated using nuclear magnetic resonance, mass and infra-red spectral data.

DOI: 10.1093/chromsci/bmab117
PMCID: PMC9439945
PMID: 34607340 [Indexed for MEDLINE]

38. **Evidence and ethical considerations for the treatment of contacts exposed to drug-resistant TB.**

Int J Tuberc Lung Dis. 2022 Sep 1;26(9):900-901. doi: 10.5588/ijtld.22.0328.

Khan U(1), Guglielmetti L(2).

DOI: 10.5588/ijtld.22.0328
PMID: 35996292 [Indexed for MEDLINE]

39. **Global trends, regional differences and age distribution for the incidence of HIV and tuberculosis co-infection from 1990 to 2019: results from the global burden of disease study 2019.**

Infect Dis (Lond). 2022 Nov;54(11):773-783. doi: 10.1080/23744235.2022.2092647. Epub 2022 Jul 7.

Wang Y(1), Jing W(1), Liu J(1), Liu M(1).

BACKGROUND: People living with human immunodeficiency virus (HIV) are more likely to develop tuberculosis (TB), and their co-infection (HIV-TB) increases the risk of death. We aimed to describe the global trends, regional differences and age distribution of HIV-TB.
METHODS: Annual new cases, age-standardized incidence rates (ASRs) and age-specific incidence rates with 95% uncertainty intervals (UIs) of HIV-infected drug-susceptible tuberculosis (HIV-DS-TB), HIV-infected multidrug-resistant tuberculosis without extensive drug resistance (HIV-MDR-TB) and HIV-infected extensively drug-resistant tuberculosis (HIV-XDR-TB) during

1990-2019 were collected from the Global Burden of Disease Study 2019. To reveal the trends of HIV-TB by region and age, the percentage change of new cases and estimated annual percentage change (EAPC) of ASRs were calculated.
RESULTS: The ASR of HIV-XDR-TB increased significantly by an average of 14.77% (95% CI: 11.05%-18.62%) per year during 1990-2019 worldwide, while the ASRs of HIV-DS-TB and HIV-MDR-TB decreased after 2005. HIV-XDR-TB was a great threat to Eastern Europe for the largest number of new cases (792, 95% UI: 487-1167) and the highest ASR (0.34 per 100,000 population, 95% UI: 0.21-0.50). In addition, Oceania had the largest rise in ASRs of HIV-MDR-TB (EAPC = 22.56, 95% CI: 18.62-26.64) and HIV-XDR-TB (EAPC = 32.95, 95% CI: 27.90-38.20) during 1990-2019. Recently, age-specific incidence rates of HIV-XDR-TB increased in all age groups, especially in the 50-69 age groups among high, low-middle and low Socio-Demographic Index regions. Additionally, the proportion of patients aged <15 years was nearly 10% of new cases in sub-Saharan Africa in 2019, which was higher than in other regions.
CONCLUSIONS: HIV-infected drug-resistant TB is common in Oceania and Eastern Europe. Moreover, HIV-XDR-TB among elderly people became increasingly prevalent. In the future, the collaboration of management for HIV and TB should be intensified in Oceania and Eastern Europe, and more concerns need to be paid in elderly people.

DOI: 10.1080/23744235.2022.2092647
PMID: 35801264 [Indexed for MEDLINE]

40. **"I would watch her with awe as she swallowed the first handful": A qualitative study of pediatric multidrug-resistant tuberculosis experiences in Durban, South Africa.**

PLoS One. 2022 Sep 16;17(9):e0274741. doi: 10.1371/journal.pone.0274741. eCollection 2022.

Misra S(1), Misra N(2), Seepamore B(3), Holloway K(2), Singh N(2), Ngozo J(4), Dlamini V(5), Radebe Z(4), Ndjeka NO(6), Furin J(7)(8).

BACKGROUND: There are limited data on the experiences of children being treated for drug-resistant tuberculosis (DR-TB), and most work in the area has been done with older children and adolescents. Comprehensive explorations of the caregiver experiences in this area are also lacking.
OBJECTIVE: To describe the experiences of being treated for drug-resistant tuberculosis of children and their caregivers.
METHODS: This was a qualitative study done using focus group discussions (FGDs) among three different groups of participants: 1) health care providers involved in the care of children being treated for DR-TB (including physicians, nurses,

and pharmacists)-herein referred to as providers; 2) household caregivers of children being treated for DR-TB-herein referred to as caregivers; and 3) children who were being treated for DR-TB-herein referred to as children. The population was a convenience sample and included children hospitalized between January 1, 2018, and June 30, 2020, ages 0-14 years old, as well as their caregivers and providers. Focus group transcripts and notes were analysed using a thematic network analysis based in grounded theory The analysis was iterative and the coding system developed focused on "stressful experiences" as well as ways to address them along the diagnostic and treatment journey. This paper follows the COREQ guidelines.
RESULTS: 16 children between the ages 7 and 14 years participated in 5 FGDs, 30 caregivers participated in 7 FGDs, and 12 providers participated in 3 FDGs. Data from the children and the caregivers were the focus of this analysis, although some themes were informed by the discussions with the providers as well. In general, it was reported that for a child diagnosed with DR-TB, there is a lived experience of stress that impacts their physical, mental, and social well-being. These pediatric patients and their families therefore develop strategies for coping with these disruptions to their lives. In general, there were major disruptive experiences that resulted from the process around receiving a diagnosis of DR-TB and second distinct set of stressful experiences that occurred during the treatment of DR-TB once the diagnosis had been made. These stresses occur in the physical, mental, and social realms, and families develop multiple strategies to cope with them, demonstrating resilience in the face of this disease.
CONCLUSION: Addressing the stresses experienced by children and their caregivers through child-friendly DR-TB testing, treatment, and counseling is not only essential for ending TB but also for enacting a human-rights based approach to child health in general. Children with DR-TB are a vulnerable population, and they have often been the last to benefit from advances in general pediatric care and in DR-TB care more specifically.

DOI: 10.1371/journal.pone.0274741
PMCID: PMC9481007
PMID: 36112604

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

41. **One-pot synthesis of α-Linolenic acid nanoemulsion-templated drug-loaded silica mesocomposites as efficient bactericide against drug-resistant Mycobacterium tuberculosis.**

Eur J Pharm Sci. 2022 Sep 1;176:106261. doi: 10.1016/j.ejps.2022.106261. Epub

2022 Jul 15.

Zhu P(1), Cai L(1), Liu Q(2), Feng S(3), Ruan H(3), Zhang L(1), Zhou L(1), Jiang H(4), Wang H(5), Wang J(6), Chen J(7).

Nowadays, pathogenic infection has posed a severe threat to the public health and environmental sanitation, urging a continuous search of efficacious and safe bactericidal agents of various formulated forms. Here, a facile one-pot hydrothermal preparation of mesoporous silica nanoparticles using ultrasonication-assisted nanoemulsion of α-Linolenic acid (α-LA) as template was developed. The formed silica mesocomposite at water/fatty-acid surface provides an easy yet green synthesis route, which can be generalized for the further encapsulation of hydrophobic drugs such as antimycobacterial Rifampicin (RIF). The obtained α-LA nanoemulsion-templated silica nanoparticles (LNS NPs), with a weight content of ∼17% α-LA in the composite, showed apparent antibacterial effect against Staphylococcus aureus (S. aureus). By comparison, the removal of α-LA from the silica nanoparticles (LNS-1 NPs) resulted in the composite of enlarged pore size with negligible bactericidal activities. Notably, the Isoniazide (INH) and Rifampicin (RIF)-encapsulated LNS NPs exhibited outstanding antimycobacterial activity against both drug-sensitive and drug-resistant Mycobacterium tuberculosis (M. tuberculosis). The obtained highly biocompatible, biosafe and low-energy consumptive α-LA-contained mesostructured silica-based bactericide holds promising therapeutic potentials to tackle the emerging drug-resistant infectious microbes.

DOI: 10.1016/j.ejps.2022.106261
PMID: 35840102 [Indexed for MEDLINE]

42. **A CRISPR-guided mutagenic DNA polymerase strategy for the detection of antibiotic-resistant mutations in M. tuberculosis.**

Mol Ther Nucleic Acids. 2022 Jul 12;29:354-367. doi: 10.1016/j.omtn.2022.07.004. eCollection 2022 Sep 13.

Feng S(1)(2)(3), Liang L(1)(2)(3), Shen C(4)(5), Lin D(1)(2)(3), Li J(1)(2)(3), Lyu L(1)(2)(3), Liang W(1)(2)(3), Zhong LL(1)(2)(3), Cook GM(6)(7), Doi Y(8)(9), Chen C(4)(5), Tian GB(1)(2)(3)(10).

A sharp increase in multidrug-resistant tuberculosis (MDR-TB) threatens human health. Spontaneous mutation in essential gene confers an ability of Mycobacterium tuberculosis resistance to anti-TB drugs. However, conventional

laboratory strategies for identification and prediction of the mutations in this slowly growing species remain challenging. Here, by combining XCas9 nickase and the error-prone DNA polymerase A from M. tuberculosis, we constructed a CRISPR-guided DNA polymerase system, CAMPER, for effective site-directed mutagenesis of drug-target genes in mycobacteria. CAMPER was able to generate mutagenesis of all nucleotides at user-defined loci, and its bidirectional mutagenesis at nick sites allowed editing windows with lengths up to 80 nucleotides. Mutagenesis of drug-targeted genes in Mycobacterium smegmatis and M. tuberculosis with this system significantly increased the fraction of the antibiotic-resistant bacterial population to a level approximately 60- to 120-fold higher than that in unedited cells. Moreover, this strategy could facilitate the discovery of the mutation conferring antibiotic resistance and enable a rapid verification of the growth phenotype-mutation genotype association. Our data demonstrate that CAMPER facilitates targeted mutagenesis of genomic loci and thus may be useful for broad functions such as resistance prediction and development of novel TB therapies.

DOI: 10.1016/j.omtn.2022.07.004
PMCID: PMC9358013
PMID: 35950213

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

43. **Minimum inhibitory concentrations of rifampin and isoniazid among multidrug and isoniazid resistant Mycobacterium tuberculosis in Ethiopia.**

PLoS One. 2022 Sep 13;17(9):e0274426. doi: 10.1371/journal.pone.0274426. eCollection 2022.

Getahun M(1)(2), Blumberg HM(3), Ameni G(4)(5), Beyene D(2), Kempker RR(3).

INTRODUCTION: Traditionally, single critical concentrations of drugs are utilized for Mycobacterium tuberculosis (Mtb) drug susceptibility testing (DST); however, the level of drug resistance can impact treatment choices and outcomes. Mutations at the katG gene are the major genetic mutations in multidrug resistant (MDR) Mtb and usually associated with high level resistance. We assessed the minimum inhibitory concentrations (MICs) of MDR or rifampin resistant (RR) and isoniazid (INH) resistant Mtb isolates to determine the quantification of drug resistance among key anti-tuberculosis drugs.
METHODS: The study was conducted on stored Mtb isolates collected as part of a national drug resistance survey in Ethiopia. MIC values were determined using

Sensititre™ MYCOTB plates. A line probe assay (MTBDRplus) was also performed to identify genetic determinants of resistance for all isolates.
RESULTS: MIC testing was performed on 74 Mtb isolates including 46 MDR, 2 RR and 26 INH phenotypically resistant isolates as determined by the Löwenstein Jensen (LJ) method. Four (15%) INH resistant Mtb isolates were detected as borderline rifampin resistance (MIC = 1 μg/ml) using MYCOTB MIC plates and no rifampin resistance mutations were detected by LPA. Among the 48 MDR/RR TB cases, 9 (19%) were rifabutin susceptible (MIC was between ≤0.25 and 0.5μg/ml). Additionally, the MIC for isoniazid was between 2-4 μg/ml (moderate resistance) for 58% of MDR TB isolates and 95.6% (n = 25) of the isolates had mutations at the katG gene.
CONCLUSION: Our findings suggest a role for rifabutin treatment in a subset of RR TB patients, thus potentially preserving an important drug class. The high proportion of moderate level INH resistant among MDR Mtb isolates indicates the potential benefit of high dose isoniazid treatment in a high proportion of katG gene harboring MDR Mtb isolates.

DOI: 10.1371/journal.pone.0274426
PMCID: PMC9469996
PMID: 36099255 [Indexed for MEDLINE]

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

44. **Phosphatidylcholine (18:0/20:4), a potential biomarker to predict ethionamide-induced hepatic steatosis in rats.**

J Appl Toxicol. 2022 Sep;42(9):1533-1547. doi: 10.1002/jat.4324. Epub 2022 Mar 29.

Muta K(1), Saito K(2), Kemmochi Y(1), Masuyama T(1), Kobayashi A(1), Saito Y(2), Sugai S(1).

Ethionamide (ETH), a second-line drug for multidrug-resistant tuberculosis, is known to cause hepatic steatosis in rats and humans. To investigate predictive biomarkers for ETH-induced steatosis, we performed lipidomics analysis using plasma and liver samples collected from rats treated orally with ETH at 30 and 100 mg/kg for 14 days. The ETH-treated rats developed hepatic steatosis with Oil Red O staining-positive vacuolation in the centrilobular hepatocytes accompanied by increased hepatic contents of triglycerides (TG) and decreased plasma TG and total cholesterol levels. A multivariate analysis for lipid profiles revealed differences in each of the 35 lipid species in the plasma and liver between the control and the ETH-treated rats. Of those lipids, phosphatidylcholine (PC) (18:0/20:4) decreased dose-dependently in both the plasma and liver. Moreover,

serum TG-rich very low-density lipoprotein (VLDL) levels, especially the large particle fraction of VLDL composed of PC containing arachidonic acid (20:4) involved in hepatic secretion of TG, were decreased dose-dependently. In conclusion, the decreased PC (18:0/20:4) in the liver, possibly leading to suppression of hepatic TG secretion, was considered to be involved in the pathogenesis of the ETH-induced hepatic steatosis. Therefore, plasma PC (18:0/20:4) levels are proposed as mechanism-related biomarkers for ETH-induced hepatic steatosis.

DOI: 10.1002/jat.4324
PMID: 35315511 [Indexed for MEDLINE]

45. **Responding to WHO´s 4-month regimen for drug-susceptible pulmonary TB.**

Int J Tuberc Lung Dis. 2022 Sep 1;26(9):898-899. doi: 10.5588/ijtld.22.0313.

Mohapatra PR(1), Mishra B(1), Dutta A(1), Bhuniya S(1).

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DOI: 10.5588/ijtld.22.0313
PMID: 35996294 [Indexed for MEDLINE]

46. **Population structure of Mycobacterium tuberculosis from referral clinics in Western Siberia, Russia: Before and during the Covid-19 pandemic.**

Infect Genet Evol. 2022 Sep;103:105343. doi: 10.1016/j.meegid.2022.105343. Epub 2022 Jul 24.

Vyazovaya A(1), Felker I(2), Schwartz Y(2), Mokrousov I(3).

The dramatic change in global health imposed by the Covid-19 pandemic has also impacted TB control. The TB incidence decreased dramatically not because of the improved situation but due to undertesting, reduced resources, and ultimately, substantially reduced detection rate. We hypothesized that multiple and partly counteracting factors could influence changes in the local Mycobacterium tuberculosis population. To test this hypothesis, we analyzed M. tuberculosis

isolates collected in Western Siberia, Russia, before and during the Covid-19 pandemic. A total of 269 M. tuberculosis isolates from patients admitted at referral clinics were studied. The pre-pandemic and pandemic collections included 179 and 90 isolates, respectively. Based on genotyping, both pre-pandemic and pandemic samples are heavily dominated by the Beijing genotype isolates (95% and 88%) that were mostly MDR (80 and 68%). The high proportion of MDR isolates is due to the specific features of the studied collections biased towards patients with severe TB admitted at the National referral center in Novosibirsk. While no dramatic change was observed in the M. tuberculosis population structure in the survey area in Western Siberia during the Covid-19 pandemic in 2020-2021 compared to the pre-pandemic collection, still we note a certain decrease of the Beijing genotype and an increase in the proportion and diversity of the non-Beijing isolates. However, the transmissible and MDR Beijing B0/W148 did not increase its prevalence rate during the pandemic. More generally, the high prevalence rate of the Beijing genotype and its strong association with MDR both before and during the pandemic are alarming features of this region in Western Siberia, Russia.

DOI: 10.1016/j.meegid.2022.105343
PMCID: PMC9308567
PMID: 35896142 [Indexed for MEDLINE]

Conflict of interest statement: None.

47. **Investigating resistance in clinical Mycobacterium tuberculosis complex isolates with genomic and phenotypic antimicrobial susceptibility testing: a multicentre observational study.**

Lancet Microbe. 2022 Sep;3(9):e672-e682. doi: 10.1016/S2666-5247(22)00116-1. Epub 2022 Jul 27.

Finci I(1), Albertini A(2), Merker M(3), Andres S(4), Bablishvili N(5), Barilar I(6), Cáceres T(7), Crudu V(8), Gotuzzo E(7), Hapeela N(9), Hoffmann H(10), Hoogland C(2), Kohl TA(6), Kranzer K(11), Mantsoki A(2), Maurer FP(12), Nicol MP(13), Noroc E(8), Plesnik S(14), Rodwell T(15), Ruhwald M(2), Savidge T(16), Salfinger M(17), Streicher E(18), Tukvadze N(5), Warren R(18), Zemanay W(9), Zurek A(19), Niemann S(6), Denkinger CM(20).

BACKGROUND: Whole-genome sequencing (WGS) of Mycobacterium tuberculosis complex has become an important tool in diagnosis and management of drug-resistant tuberculosis. However, data correlating resistance genotype with quantitative

phenotypic antimicrobial susceptibility testing (AST) are scarce.
METHODS: In a prospective multicentre observational study, 900 clinical M tuberculosis complex isolates were collected from adults with drug-resistant tuberculosis in five high-endemic tuberculosis settings around the world (Georgia, Moldova, Peru, South Africa, and Viet Nam) between Dec 5, 2014, and Dec 12, 2017. Minimum inhibitory concentrations (MICs) and resulting binary phenotypic AST results for up to nine antituberculosis drugs were determined and correlated with resistance-conferring mutations identified by WGS.
FINDINGS: Considering WHO-endorsed critical concentrations as reference, WGS had high accuracy for prediction of resistance to isoniazid (sensitivity 98·8% [95% CI 98·5-99·0]; specificity 96·6% [95% CI 95·2-97·9]), levofloxacin (sensitivity 94·8% [93·3-97·6]; specificity 97·1% [96·7-97·6]), kanamycin (sensitivity 96·1% [95·4-96·8]; specificity 95·0% [94·4-95·7]), amikacin (sensitivity 97·2% [96·4-98·1]; specificity 98·6% [98·3-98·9]), and capreomycin (sensitivity 93·1% [90·0-96·3]; specificity 98·3% [98·0-98·7]). For rifampicin, pyrazinamide, and ethambutol, the specificity of resistance prediction was suboptimal (64·0% [61·0-67·1], 83·8% [81·0-86·5], and 40·1% [37·4-42·9], respectively). Specificity for rifampicin increased to 83·9% when borderline mutations with MICs overlapping with the critical concentration were excluded. Consequently, we highlighted mutations in M tuberculosis complex isolates that are often falsely identified as susceptible by phenotypic AST, and we identified potential novel resistance-conferring mutations.
INTERPRETATION: The combined analysis of mutations and quantitative phenotypes shows the potential of WGS to produce a refined interpretation of resistance, which is needed for individualised therapy, and eventually could allow differential drug dosing. However, variability of MIC data for some M tuberculosis complex isolates carrying identical mutations also reveals limitations of our understanding of the genotype and phenotype relationships (eg, including epistasis and strain genetic background).
FUNDING: Bill & Melinda Gates Foundation, German Centre for Infection Research, German Research Foundation, Excellence Cluster Precision Medicine of Inflammation (EXC 2167), and Leibniz ScienceCampus EvoLUNG.

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PMCID: PMC9436784
PMID: 35907429 [Indexed for MEDLINE]

Conflict of interest statement: Declaration of interests MM and SN report grants from the German Center for Infection Research, Excellenz Cluster Precision Medicine in Chronic Inflammation, and Leibniz Science Campus Evolutionary

Medicine of the LUNG (EvoLUNG). TR reports personal fees from FIND, grants from the US National Institute of Allergy and Infectious Diseases, and is a board member for Verus Diagnostics; and has a provisional patent (#63/048.989) and a pending patent (#14840432.0) for tuberculosis diagnostics. All other authors declare no competing interests.

48. **[Expert consensus on clinical application of delamanid].**

Zhonghua Jie He He Hu Xi Za Zhi. 2022 Sep 12;45(9):872-880. doi: 10.3760/cma.j.cn112147-20220422-00344.

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

Chinese Society of Tuberculosis, Chinese Medical Association.

Multidrug-resistant tuberculosis(MDR-TB) is a major problem in the prevention and treatment of tuberculosis worldwide, but the treatment success rate is low, and it is necessary to develop new anti-tuberculosis drugs and optimize treatment. Delamanid, a drug with good activity against MDR-TB, has been marketed in recent years. However, there is a lack of clinical medication guidance of delamanid for tuberculosis treatment. To standardize the rational application of delamanid in clinical practice, Chinese Tuberculosis Society organized experts in related fields to issue this consensus. This consensus described the molecular structure, anti-tuberculosis mechanism, pharmacodynamics/pharmacokinetics, drug resistance mechanism, and clinical research of delamanid, put forward recommendations for clinical application, and explained its suitable population, contraindications, methods of application, adverse events, and precautions, so as to provide a reference for clinicians to use delamanid.

DOI: 10.3760/cma.j.cn112147-20220422-00344
PMID: 36097924 [Indexed for MEDLINE]

49. **Binding Thermodynamics and Dissociation Kinetics Analysis Uncover the Key Structural Motifs of Phenoxyphenol Derivatives as the Direct InhA Inhibitors and the Hotspot Residues of InhA.**

Int J Mol Sci. 2022 Sep 3;23(17):10102. doi: 10.3390/ijms231710102.

Zhang Q(1)(2), Han J(3), Zhu Y(3), Tan S(3), Liu H(1).

Given the current epidemic of multidrug-resistant tuberculosis, there is an

urgent need to develop new drugs to combat drug-resistant tuberculosis. Direct inhibitors of the InhA target do not require activation and thus can overcome drug resistance caused by mutations in drug-activating enzymes. In this work, the binding thermodynamic and kinetic information of InhA to its direct inhibitors, phenoxyphenol derivatives, were explored through multiple computer-aided drug design (CADD) strategies. The results show that the van der Waals interactions were the main driving force for protein-ligand binding, among which hydrophobic residues such as Tyr158, Phe149, Met199 and Ile202 have high energy contribution. The AHRR pharmacophore model generated by multiple ligands demonstrated that phenoxyphenol derivatives inhibitors can form pi-pi stacking and hydrophobic interactions with InhA target. In addition, the order of residence time predicted by random acceleration molecular dynamics was consistent with the experimental values. The intermediate states of these inhibitors could form hydrogen bonds and van der Waals interactions with surrounding residues during dissociation. Overall, the binding and dissociation mechanisms at the atomic level obtained in this work can provide important theoretical guidance for the development of InhA direct inhibitors with higher activity and proper residence time.

DOI: 10.3390/ijms231710102
PMCID: PMC9456180
PMID: 36077494 [Indexed for MEDLINE]

Conflict of interest statement: The researcher claims no conflicts of interests.

50. **Pretomanid in the Treatment of Patients with Tuberculosis in the United States.**

N Engl J Med. 2022 Sep 1;387(9):850-852. doi: 10.1056/NEJMc2119461.

Goswami ND(1), Ashkin D(2), Haley CA(2); BAM Project Team.

Collaborators: Colon Semidey A, Peddareddy LP, Reeter S, Wegner PL, Landers K, Khan E, Dasgupta-Tsinikas S, Yu S, Caplan-Shaw C, Oxtoby M, Jereb J, Spitters C, Gomez ME, Hammond-Epstein H, Ogawa L, DeSilva M, Sabuwala N, Hancock-Allen J, Vang MX, Cropper T, Dov LK, Narita M, Jasuja S, Dorman S, Darnell C, Gullickson C, Berman L, Darnall E, Macias P.

DOI: 10.1056/NEJMc2119461
PMID: 36053513 [Indexed for MEDLINE]

51. **Assessing Prolongation of the Corrected QT Interval with Bedaquiline and Delamanid Coadministration to Predict the Cardiac Safety of Simplified Dosing**

Regimens.

Clin Pharmacol Ther. 2022 Oct;112(4):873-881. doi: 10.1002/cpt.2685. Epub 2022 Jul 13.

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 corrected QT interval (QTc) prolongation. We aimed to investigate the relationships between the drugs' plasma concentrations and the prolongation of observed QT interval corrected using Fridericia's formula (QTcF) 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 coadministration 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% (95% confidence interval (CI), 22-40%) for M2 and 33% (95% CI, 24-54%) for DM-6705. The generated combined effect was not greater but close to "additivity" in the analyzed concentration range. Predictions with the final model suggested a similar QT prolonging potential with simplified, once-daily dosing regimens compared with the approved regimens, with a maximum median change from baseline QTcF increase of 20 milliseconds 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.

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Conflict of interest statement: Conflicts of Interest statement Study

bedaquiline and delamanid provided to NIH by Janssen and Otsuka, respectively, for the parent study. All other authors declared no competing interests for this work.

52. **Retrospective evaluation of routine whole genome sequencing of Mycobacterium tuberculosis at the Belgian National Reference Center, 2019.**

Acta Clin Belg. 2022 Oct;77(5):853-860. doi: 10.1080/17843286.2021.1999588. Epub 2021 Nov 9.

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OBJECTIVES: Since January 2019, the Belgian National Reference Center for Mycobacteria (NRC) has switched from conventional typing to prospective whole-genome sequencing (WGS) of all submitted Mycobacterium tuberculosis complex (MTB) isolates. The ISO17025 validated procedure starts with semi-automated extraction and purification of gDNA directly from the submitted MGIT tubes, without preceding subculturing. All samples are then sequenced on an Illumina MiSeq sequencer and analyzed using an in-house developed and validated bioinformatics workflow to determine the species and antimicrobial resistance. In this study, we retrospectively compare results obtained via WGS to conventional phenotypic and genotypic testing, for all Belgian MTB strains analyzed in 2019 (n = 306).
RESULTS: In all cases, the WGS-based procedure was able to identify correctly the MTB species. Compared to MGIT drug susceptibility testing (DST), the sensitivity and specificity of genetic prediction of resistance to first-line antibiotics were respectively 100 and 99% (rifampicin, RIF), 90.5 and 100% (isoniazid, INH), 100 and 98% (ethambutol, EMB) and 61.1 and 100% (pyrazinamide, PZA). The negative predictive value was above 95% for these four first-line drugs. A positive predictive value of 100% was calculated for INH and PZA, 80% for RIF and 45% for EMB.
CONCLUSIONS: Our study confirms the effectiveness of WGS for the rapid detection of M. tuberculosis complex and its drug resistance profiles for first-line drugs even when working directly on MGIT tubes, and supports the introduction of this test into the routine workflow of laboratories performing tuberculosis diagnosis.

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PMID: 34751641 [Indexed for MEDLINE]

53. **Pharmacokinetics and Safety of WHO-Recommended Dosage and Higher Dosage of Levofloxacin for Tuberculosis Treatment in Children: a Pilot Study.**

Int J Infect Dis. 2022 Sep;122:603-608. doi: 10.1016/j.ijid.2022.07.029. Epub 2022 Jul 13.

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OBJECTIVES: To evaluate the pharmacokinetic parameters of the 2020 World Health Organization (WHO)-recommended pediatric dosage of levofloxacin and the higher-than-WHO dosage.
METHODS: Children aged 1-15 years with tuberculosis who received levofloxacin-based treatment for at least 7 days were enrolled. First, five children were enrolled to receive the WHO-recommended dosage (15-20 mg/kg/day), then an additional five children received a dosage higher than the WHO-recommended dosage (20-30 mg/kg/day). Blood samples were collected at predose and postdose 1, 2, 4, 6, 8, and 12 hours. A target of the ratio of the free area under the concentration-time curve to minimum inhibitory concentration (fAUC/MIC) was 100.
RESULTS: The median (interquartile range) age was 9.6 (4.9-10.5) and 12.0 (10.1-12.3) years in the WHO dosage and higher-than-WHO dosage groups, respectively. The median (interquartile range) duration of antituberculosis treatment was 24 (8-24) weeks. The geometric mean (95% confidence interval) of fAUC/MIC was 60.4 (43.5-84.0) and 103.2 (70.1-151.8) in the WHO and higher-than-WHO dosage groups, respectively. There was no adverse event of QT prolongation or any other grade 3 or 4 adverse events.
CONCLUSION: Levofloxacin at a higher dose of 20-30 mg/kg/day could achieve the fAUC/MIC target in children.

DOI: 10.1016/j.ijid.2022.07.029
PMID: 35842213 [Indexed for MEDLINE]

Conflict of interest statement: Declaration of Competing Interest The authors have no competing interests to declare.

54. **Socioeconomic disparities and multidrug-resistant tuberculosis in South Korea: Focus on immigrants and income levels.**

J Microbiol Immunol Infect. 2022 Sep 7:S1684-1182(22)00143-8. doi:

10.1016/j.jmii.2022.08.014. Online ahead of print.

Jeong HE(1), Bea S(2), Kim JH(1), Jang SH(3), Son H(4), Shin JY(5).

Risk factors of MDR-TB remain unclear in South Korea, despite being an important public health issue. Findings from this study, which included ≥50,000 patients with TB from South Korea, suggests that immigrants and patients with lower income levels were strong predictors of MDR-TB in a high-income, high TB incidence country.

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PMID: 36115791

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

55. **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).

News

1. https://www.tbonline.info/posts/2022/9/12/new-global-fund-report-shows-50-million-lives-save/
   New Global Fund report shows 50 million lives saved over 20 years in fight against HIV, TB and malaria; Pandemic investments paying off

   The Global Fund's 2022 Results Report released today finds a significant rebound in 2021 for programs working to defeat HIV, tuberculosis (TB) and malaria. In 2020, the COVID-19 pandemic had a devastating impact on the fight against the three diseases, leading to the decline of key programmatic results across the three diseases for the first time in the history of the Global Fund. When the pandemic hit countries where the Global Fund works, the partnership rapidly mounted a response to deliver additional resources. This year, the new report shows those investments paid off and recovery is underway.

2. https://www.tballiance.org.za/news/zenix-new-england-journal-medicine
   Drug-Resistant TB Trial Results Published in New England Journal of Medicine

   The results of ZeNix, a Phase 3 clinical trial that took place in 11 sites across Georgia, Moldova, Russia, and South Africa, revealed that the BPaL treatment remains effective against highly drug-resistant strains of tuberculosis (TB) with reduced dosage and/or duration of the linezolid component of the regimen.1 Along with the maintenance of efficacy, there was a decrease in linezolid-associated side effects that accompanied the reduced dosage or duration of linezolid.1 The results from the trial, which was led by TB Alliance, a non-profit TB drug developer, were published today in the New England Journal of Medicine.

3. https://www.tbonline.info/posts/2022/9/14/using-artificial-intelligence-improve-tb-treatment/#
   Tufts scientists use artificial intelligence to improve TB treatments

   Imagine you have 20 new compounds that have shown some effectiveness in treating a disease like tuberculosis (TB), which affects 10 million people worldwide and kills 1.5 million each year. You know that to treat the disease effectively, patients will need a combination of three or four drugs because TB bacteria behave differently in different environments—and in some cases, evolve to become drug-resistant. How do you decide which drugs to test together? Twenty compounds in three- and four-drug combinations offer nearly 6,000 possible combinations. In a recent study, published in the September issue of Cell Reports Medicine, researchers from Tufts University used machine learning to design a data-driven solution to this challenge that will allow researchers to consider novel drug combinations at a new scale. They believe their new system can increase the speed at which scientists determine which drug combinations will most effectively treat tuberculosis, the second leading infectious killer in the world.

4. https://www.tbonline.info/posts/2022/9/16/new-test-uses-nanotechnology-artificial-intelligen/
   New test uses nanotechnology, artificial intelligence to diagnose TB in children

   A new blood test developed by Tulane University researchers combines nanotechnology with artificial intelligence to diagnose tuberculosis (TB) in children in instances when the deadly disease might otherwise go undetected, according to a study in Nature Biomedical Engineering. Although the current test requires a sophisticated lab to perform, researchers are working to streamline it so it can be performed in the community and read with a smartphone.

5. https://www.tbonline.info/posts/2022/9/14/msf-warns-supply-delays-critical-tb-test-will-cost/
   MSF warns that supply delays of critical TB test will cost lives

   The Stop TB Partnership's Global Drug Facility (GDF) communicated today (14 September 2022) that there could be significant supply delays of the critical GeneXpert TB test due to production constraints by Cepheid, the US based corporation that produces the test. The communication says that the delays are caused by COVID supply chain challenges and an increasing demand for GeneXpert TB tests. Countries placing larger orders may face delays of up to 6 months. The backlog of orders for TB tests is expected to last through March 2023. GDF facilitates global access to quality-assured TB diagnostics and treatments through a one-stop procurement and supply mechanism for national TB programs.