PubMed Open Access

1. Effect of Stenotrophomonas maltophilia on Tuberculosis.

Microbiol Spectr. 2023 Aug 17;11(4):e0094423. doi: 10.1128/spectrum.00944-23. Epub 2023 Jun 12.

Li Y(1), Zhao A(2), Yu Q(2), Yu N(2), Cui Y(1), Ma X(1), Liu H(1), Wang R(1).

Tuberculosis (TB) is an important infectious disease suffered by many countries, including China. In this stage, accurate diagnosis and treatment are key measures for the prevention and control of TB. Stenotrophomonas maltophilia is a global emerging Gram-negative, multidrug-resistant (MDR) organism characterized by its high contribution to the increase in crude mortality rates. By single cell preparation and strain identification, we isolated S. maltophilia from stored cultures of Mycobacterium tuberculosis (Mtb). We found that S. maltophilia could not be removed from sputum by alkali treatment or inhibited by antibiotic mixture added to MGIT 960 indicator tubes. When co-cultured with Mtb on a Löwenstein-Jensen (L-J) slant, it could inhibit the growth of Mtb and liquefy the medium. More seriously, it was resistant to 10 of the 12 anti-TB drugs, including isoniazid and rifampin, and made the mixed samples display multidrug-resistant Mtb (MDR-TB) results in the drug sensitivity test, which might change a treatment regimen and increase disease burden. Following, we conducted a small-scale surveillance which showed that the isolation rate of S. maltophilia in TB patients was 6.74%, but these patients had no special characteristics and the presence of S. maltophilia was hidden. The effect of S. maltophilus on TB and its mechanism are unclear and require more attention. IMPORTANCE China is a high-burden country for tuberculosis (TB), multidrug-resistant/rifampicin-resistant tuberculosis (MDR/RR-TB), and HIV-associated TB. Increasing the positive rate of culture and the accuracy of antibiotic susceptibility testing (AST) are important for diagnosis, treatment, and control of TB. In our study, we found that the isolation rate of Stenotrophomonas maltophilia in TB patients was not neglectable and that this bacterium affects the isolation and AST results of TB. Due to a lack of relevant research, the impact of S. maltophilia on the course and outcome of TB is unclear. However, the characteristics of S. maltophilia that increase disease mortality require attention. Therefore, in the clinical testing of TB, in addition to mycobacteria, it is recommended to increase the detection of co-infected bacteria and improve the awareness of TB clinicians of these bacteria.

DOI: 10.1128/spectrum.00944-23
PMCID: PMC10433947
PMID: 37306591 [Indexed for MEDLINE]

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

2. Whole genome sequencing of drug resistance Mycobacterium tuberculosis from extra-pulmonary sites.

Life Sci Alliance. 2023 Aug 17;6(11):e202302076. doi: 10.26508/lsa.202302076. Print 2023 Nov.

Shi T(1), Shou F(2), He Y(3), Zhou K(3), Gao W(3), Nie X(4), Han M(3), Liao C(5), Li T(6).

This study aimed to determinate characteristics of drug resistance Mycobacterium tuberculosis from patients with extra-pulmonary tuberculosis (EPTB). Patients were retrospectively studied from January 2020 to December 2021. All the isolates were cultured, tested drug susceptibility, and detected the gene mutation using whole genome sequencing. The correlations of whole genome sequencing, pattern of DR, patients' distribution, and transmission were analyzed. 111 DR-EPTB isolates included pre-XDR-TB (53.2%), MDR-TB (29.7%), and poly-DR-TB (12.6%). The resistant drugs were INH followed by RFP and SM. The genotypes of 111 strains were lineage 2 and lineage 4. KatG_p.Ser315Thr was main gene mutation for resistance to INH; rpsL_p.Lys43Arg for SM, rpoB_p.Ser450Leu for rifampicin, embB_p.Met306Val for ethambutol, gyrA_p.Asp94Gly for FQs, and pncA_p.Thr76Pro for PZA. The residence was a significant risk factor for cluster transmission by patients and phenotypic DR types of strains for lineage 2 transmission. In the local area of southwest China INH, rifampicin and SM were main drugs in patients with DR-EPTB. KatG_p.Ser315, rpoB_p.Ser450Leu, and rpsL_p.Lys43Arg were main gene mutations. Phenotypic DR types and residence were main risk of transmission.

DOI: 10.26508/lsa.202302076
PMCID: PMC10435967
PMID: 37591723 [Indexed for MEDLINE]

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

3. Adolescence, multidrug resistant tuberculosis, bedaquine and videotapes.

An Pediatr (Engl Ed). 2023 Aug;99(2):150-151. doi: 10.1016/j.anpede.2023.01.016.

Epub 2023 Jun 22.

Gamell A(1), Latre C(2), López-Ramos MG(2), Noguera-Julian A(3).

DOI: 10.1016/j.anpede.2023.01.016
PMID: 37355456 [Indexed for MEDLINE]

4. Evaluation of Xpert MTB/XDR test for susceptibility testing of Mycobacterium tuberculosis to first and second-line drugs in Uganda.

PLoS One. 2023 Aug 17;18(8):e0284545. doi: 10.1371/journal.pone.0284545. eCollection 2023.

Katamba A(1), Ssengooba W(2)(3)(4), Sserubiri J(2)(4), Semugenze D(2)(4), Kasule GW(5), Nyombi A(5), Byaruhanga R(5), Turyahabwe S(5), Joloba ML(2)(4)(5).

BACKGROUND: Drug-Resistant Tuberculosis (DR-TB) is one of the major challenges to TB control.
DESIGN AND METHODS: This was a blinded, laboratory-based cross-sectional study using sputum samples or culture isolates. Samples were from patients with rifampicin-resistant-TB and/or with high risk for isoniazid (INH) resistance and/or 2nd line fluoroquinolones (FQ) and injectable agents (IAs). The diagnostic accuracy of the Xpert® MTB/XDR test was compared to MGIT960 and the Hain Genotype® MTBDRplus and MDRsl assays (LPA) as reference DST methods. Factors for laboratory uptake of the Xpert® MTB/XDR test were also evaluated.
RESULTS: Of the 100 stored sputum samples included in this study, 65/99 (65.6%) were resistant to INH, 5/100 (5.0%) were resistant to FQ and none were resistant to IAs using MGIT960. The sensitivity and specificity, n (%; 95% Confidence Interval, CI) of Xpert® MTB/XDR test for; INH was 58 (89.2; 79.1-95.5) and 30 (88.2; 72.5-96.6) and for FQ; 4 (80.0; 28.3-99.4) and 95 (100; 96.2-100), respectively. Using LPA as a reference standard, a total of 52/98 (53.1%) were resistant to INH, 3/100 (3.0%) to FQ, and none to IA. The sensitivity and specificity, n (%; 95%CI) of Xpert® MTB/XDR test compared to LPA for; INH was 50 (96.1; 86.7-99.5) and 34 (74.0; 58.8-85.7) for FQ 3 (100; 29.2-100) and 96 (99.0; 94.3-99.9) respectively. The factors for laboratory uptake and roll-out of the Xpert® MTB/XDR test included: no training needed for technicians with, and one day for those without, previous Xpert-ultra experience, recording and reporting needs were not different from those of Xpert-ultra, the error rate was 4/100 (4%), one (1%) indeterminate rate and test turn-around-time were 1hr/45 minutes.
CONCLUSION: There is high sensitivity and specificity of Xpert® MTB/XDR test for isoniazid and fluoroquinolones. There are acceptable Xpert® MTB/XDR test attributes for the test uptake and roll-out.

DOI: 10.1371/journal.pone.0284545
PMCID: PMC10434885
PMID: 37590288 [Indexed for MEDLINE]

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

5. Treatment of drug-resistant tuberculosis in children and young adolescents in Brazil.

J Clin Tuberc Other Mycobact Dis. 2023 Aug 2;33:100388. doi: 10.1016/j.jctube.2023.100388. eCollection 2023 Dec.

Bruzadelli Paulino da Costa F(1), Zamboni Berra T(1), Garcia de Almeida Ballestero J(1), Bartholomay Oliveira P(2), Maria Pelissari D(3), Mathias Alves Y(1), Carlos Vieira Ramos A(1), Queiroz Rocha de Paiva J(4), Kehinde Ayandeyi Teibo T(1), Alexandre Arcêncio R(1).

INTRODUCTION: Drug-resistant tuberculosis (DR-TB) is a global threat and a challenge for public health authorities worldwide. In children, the diagnosis is even more challenging and DR-TB is poorly described in the literature, as are its treatment outcomes. In this study, we aimed to describe the treatment of drug-resistant TB in children and young adolescents in Brazil.
METHODS: A descriptive epidemiological study of treatment for DR-TB in children under 15 years of age in Brazil between 2013 and 2020. The primary data source was the Information System for Special Tuberculosis Treatments (SITE-TB). Categorical variables were analyzed using relative frequencies (%) and continuous variables by measures of central tendency to characterize the profile of the cases, namely: sociodemographic, clinical characteristics, procedures, tests performed and treatment success. In order to verify the distribution of cases, a spatial analysis was carried out based on the municipality where the cases resided.
RESULTS: Between 2013 and 2020, 19,757 tuberculosis (TB) cases occurred in children aged <15 years in Brazil, and 46 cases of treatment for DR-TB were reported during the same period (annual average of 6 cases). Of these, 73.9% were aged 10-14, 65.2% were male, 4.3% were HIV+ and 43.3% were underweight (BMI<18.5) at the start of treatment. 17.4% had previous contact with TB, 69.6%

had primary resistance, 47.8% multidrug resistance. The median duration of treatment was 15 months. DOT and standardized treatment regimen were performed in 52.2% of cases. Bacilloscopy was performed for 97.8% (57.8% positive); culture for 89.1% (75.6% positive), rapid molecular test for 73.9% with proven resistance to rifampicin in 55.8%. Susceptibility testing revealed resistance mainly to isoniazid (87.8%) and rifampicin (60.6%). 73.9% of cases were successfully treated and one death was reported. Cases were treated in 26 Brazilian municipalities, with the majority in Rio de Janeiro (15) and São Paulo (4).
CONCLUSION: DR-TB treatment was recorded in <1% of general TB cases in children and young adolescents, suggesting underreporting of drug-resistant cases in the country. Despite the low number of registered cases, the data reflect the situation of DR-TB in this population and describe important aspects of the problem, as the child needs comprehensive, individualized care, with support from different professionals. We recommend a strengthening of the country's referral services for the care of children with DR-TB so that surveillance and health care services can work together to identify and follow up cases.

DOI: 10.1016/j.jctube.2023.100388
PMCID: PMC10425933
PMID: 37588725

Conflict of interest statement: The authors declare that they have no known competing financial interests or personal relationships that might appear to influence the work reported in this article.Although the cited agencies supported the research, the funders had no role in the study design; in the collection, analysis, and interpretation of the data; and in the decision to submit the article for publication.

6. Clinical features, resistance patterns and treatment outcomes of drug-resistant extra-pulmonary tuberculosis: A scoping review.

J Clin Tuberc Other Mycobact Dis. 2023 Aug 4;33:100390. doi: 10.1016/j.jctube.2023.100390. eCollection 2023 Dec.

Miiro E(1), Olum R(2), Baluku JB(3)(4).

BACKGROUND: Drug-resistant tuberculosis (DR-TB) is a threat to tuberculosis (TB) control. Extra-pulmonary forms of DR-TB (DR-epTB) are not well characterized. This review summarizes the clinical features, resistance patterns and treatment outcomes of DR-epTB.

METHODS: We searched EMBASE to identify studies that reported drug-resistance among extra-pulmonary TB sites. All age groups were included in this review. Studies which did not describe drug-resistance patterns at extra-pulmonary TB sites were excluded. We summarized the proportion of resistance to individual anti-TB drugs as well as multi-drug resistant (MDR), pre-extensively drug resistant (pre-XDR) and extensively drug-resistant (XDR) TB.
RESULTS: Eighteen studies with a total of 10,222 patients with extra-pulmonary TB of whom 1,236 (12.0%) had DR-epTB, were included in this review. DR-epTB was mostly reported in young people aged 28 to 46 years. While TB meningitis is the most commonly studied form, adenitis is the commonest form of DR-epTB reported in 21% to 47%. Central nervous system TB (3.8% to 51.6%), pleural TB (11.3% to 25.9%), skeletal TB (9.4% to 18.1%), abdominal TB (4.3% to 6.5%), and disseminated TB (3.8%) are also encountered. The HIV co-infection rate is reported to be 5.0% to 81.3% while 2.6% to 25.4 % have diabetes mellitus. Clinical symptoms of DR-epTB are consistent with morbidity in the affected body system. Among patients with DR-epTB, the proportion of MDR TB was 5% to 53% while that for pre-XDR TB and XDR TB was 3% to 40% and 4% to 33%, respectively. Treatment success is achieved in 26% to 83% of patients with DR-epTB while death, treatment loss-to-follow up, and treatment failure occur in 2% to 76%, 7% to 15%, and 0% to 4% respectively. Patients with DR-epTB were reported to have poorer outcomes than those with pulmonary DR-TB and extra-pulmonary drug-susceptible TB.
CONCLUSION: Clinical features of DR-epTB are similar to those observed among people with drug-susceptible EPTB but patients with DR-epTB post worse treatment outcomes.

DOI: 10.1016/j.jctube.2023.100390
PMCID: PMC10425399
PMID: 37588726

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.

7. Favourable outcomes in RR-TB patients using BPaL and other WHO-recommended second-line anti-TB drugs.

Int J Tuberc Lung Dis. 2023 Aug 1;27(8):599-605. doi: 10.5588/ijtld.22.0649.

Rikhotso MC(1), Ledwaba SE(1), Ngandu JK(1), Mavumengwana V(2), Kinnear CJ(2), Warren R(2), Potgieter N(1), Traoré AN(1).

SETTING: According to reports in South Africa, treatment failure rates for rifampicin-resistant TB (RR-TB) are significant and below the WHO target of ≥70%. HIV infection and the use of highly active antiretroviral therapy (HAART) influence how patients receiving anti-TB drugs respond to therapy. In the treatment of RR-TB, more recent medications, including bedaquiline, pretomanid and linezolid (BPaL), have shown promising results.OBJECTIVE: To assess treatment outcomes in RR-TB patients using BPaL and other second-line anti-TB drugs as recommended by the WHO in the South African population.DESIGN: The databases Medline, PubMed, Google Scholar and Embase were searched for studies between 2015 and 2022, which investigated BPaL outcomes in South Africa.RESULTS: Of the 27,259 participants, 21% were on bedaquiline, 1% were taking pretomanid and 9% were taking linezolid as part of their background regimen. About 68% of the patients were HIV-positive, with 59% of them taking HAART.CONCLUSION: Overall, 66% of patients taking BPaL drugs as part of their background regimen had favourable treatment outcomes. Additionally, patients with RR-TB who were HIV-positive and taking HAART while receiving BPaL drugs as part of a background regimen had improved treatment outcomes.

CONTEXTE : Selon des rapports en Afrique du Sud, les taux d'échec du traitement de la TB résistante à la rifampicine (RR-TB) sont considérables et inférieurs à l'objectif de ≥70% fixé par l'OMS. L'infection par le VIH et l'utilisation d'une thérapie antirétrovirale hautement active (HAART) influencent la manière dont les patients recevant des médicaments anti-TB répondent au traitement. Dans le traitement de la RR-TB, des médicaments plus récents, notamment la bédaquiline, le prétomanid et le linézolide (BPaL), ont donné des résultats prometteurs.
OBJECTIF : Évaluer les résultats du traitement des patients atteints de RR-TB à l'aide de BPaL et d'autres médicaments anti-TB de deuxième intention, conformément aux recommandations de l'OMS, dans la population sud-africaine.
MÉTHODE : Les bases de données Medline, PubMed, Google Scholar et Embase ont été consultées pour trouver des études réalisées entre 2015 et 2022 sur les résultats de la BPaL en Afrique du Sud.
RÉSULTATS : Sur les 27 259 participants, 21% prenaient de la bédaquiline, 1% du prétomanid et 9% du linézolide dans le cadre de leur traitement de fond. Environ 68% des patients étaient séropositifs, et 59% d'entre eux suivaient un traitement HAART.
CONCLUSION : Dans l'ensemble, 66% des patients prenant des médicaments BPaL dans le cadre de leur traitement de fond ont obtenu des résultats favorables. En outre, les patients atteints de RR-TB qui étaient séropositifs et prenaient le traitement HAART tout en recevant des médicaments BPaL dans le cadre d'un traitement de fond ont eu de meilleurs résultats thérapeutiques.

DOI: 10.5588/ijtld.22.0649
PMCID: PMC10365554

PMID: 37491748 [Indexed for MEDLINE]

Conflict of interest statement: Conflicts of interest: none declared.

8. Surveillance of multidrug-resistant tuberculosis in sub-Saharan Africa through wastewater-based epidemiology.

Heliyon. 2023 Jul 21;9(8):e18302. doi: 10.1016/j.heliyon.2023.e18302.
eCollection 2023 Aug.

Mtetwa HN(1)(2), Amoah ID(1)(3), Kumari S(1), Bux F(1), Reddy P(1)(2).

The spread of multidrug-resistant tuberculosis (MDR-TB) is a serious public health issue, particularly in developing nations. The current methods of monitoring drug-resistant TB (DR-TB) using clinical diagnoses and hospital records are insufficient due to limited healthcare access and underreporting. This study proposes using Wastewater-Based Epidemiology (WBE) to monitor DR-TB in six African countries (Ghana, Nigeria, Kenya, Uganda, Cameroon, and South Africa) and examines the impact of treated wastewater on the spread of TB drug-resistant genes in the environment. Using droplet-digital polymerase chain reaction (ddPCR), the study evaluated untreated and treated wastewater samples in selected African countries for TB surveillance. There was a statistically significant difference in concentrations of genes conferring resistance to TB drugs in wastewater samples from the selected countries (p-value<0.05); South African samples exhibited the highest concentrations of 4.3(±2,77), 4.8(±2.96), 4.4(±3,10) and 4.7(±3,39) log copies/ml for genes conferring resistance to first-line TB drugs (katG, rpoB, embB and pncA respectively) in untreated wastewater. This may be attributed to the higher prevalence of TB/MDR-TB in SA compared to other African countries. Interestingly, genes conferring resistance to second-line TB drugs such as delamanid (ddn gene) and bedaquiline (atpE gene) were detected in relatively high concentrations (4.8(±3,67 and 3.2(±2,31 log copies/ml for ddn and atpE respectively) in countries, such as Cameroon, where these drugs are not part of the MDR-TB treatment regimens, perhaps due to migration or the unapproved use of these drugs in the country. The gene encoding resistance to streptomycin (rrs gene) was abundant in all countries, perhaps due to the common use of this antibiotic for infections other than TB. These results highlight the need for additional surveillance and monitoring, such as WBE, to gather data at a community level. Combining WBE with the One Health strategy and current TB surveillance systems can help prevent the spread of DR-TB in populations.

DOI: 10.1016/j.heliyon.2023.e18302
PMCID: PMC10412881
PMID: 37576289

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.

9. Isoniazid-resistant TB: treatment outcomes and impact of regimens with fluoroquinolones.

Int J Tuberc Lung Dis. 2023 Aug 1;27(8):638-640. doi: 10.5588/ijtld.23.0107.

Silva DR(1), Muñoz-Torrico M(2), Fernandes GR(3), Narvaez-Diaz L(4), Miranda-Perez A(5), Dos Santos APC(6), Becerril-Vargas E(4), Soto-Vidal G(5), Willers DMC(7), Migliori GB(8).

DOI: 10.5588/ijtld.23.0107
PMCID: PMC10365560
PMID: 37491756 [Indexed for MEDLINE]

10. Mind the gap. Rolling out new drug resistant tuberculosis regimens with limited diagnostic tools.

J Clin Tuberc Other Mycobact Dis. 2023 Feb 4;32:100350. doi: 10.1016/j.jctube.2023.100350. eCollection 2023 Aug.

Saluzzo F(1)(2), Maria Cirillo D(1)(2).

DOI: 10.1016/j.jctube.2023.100350
PMCID: PMC10302535
PMID: 37389011

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.

11. Wollamide Cyclic Hexapeptides Synergize with Established and New Tuberculosis Antibiotics in Targeting Mycobacterium tuberculosis.

Microbiol Spectr. 2023 Aug 17;11(4):e0046523. doi: 10.1128/spectrum.00465-23.

Epub 2023 Jun 8.

Rollo RF(1), Mori G(1), Hill TA(2)(3), Hillemann D(4), Niemann S(5)(6), Homolka S(5), Fairlie DP(2)(3), Blumenthal A(1).

Shorter and more effective treatment regimens as well as new drugs are urgent priorities for reducing the immense global burden of tuberculosis (TB). As treatment of TB currently requires multiple antibiotics with diverse mechanisms of action, any new drug lead requires assessment of potential interactions with existing TB antibiotics. We previously described the discovery of wollamides, a new class of Streptomyces-derived cyclic hexapeptides with antimycobacterial activity. To further assess the value of the wollamide pharmacophore as an antimycobacterial lead, we determined wollamide interactions with first- and second-line TB antibiotics by determining fractional inhibitory combination index and zero interaction potency scores. In vitro two-way and multiway interaction analyses revealed that wollamide B1 synergizes with ethambutol, pretomanid, delamanid, and para-aminosalicylic acid in inhibiting the replication and promoting the killing of phylogenetically diverse clinical and reference strains of the Mycobacterium tuberculosis complex (MTBC). Wollamide B1 antimycobacterial activity was not compromised in multi- and extensively drug-resistant MTBC strains. Moreover, growth-inhibitory antimycobacterial activity of the combination of bedaquiline/pretomanid/linezolid was further enhanced by wollamide B1, and wollamide B1 did not compromise the antimycobacterial activity of the isoniazid/rifampicin/ethambutol combination. Collectively, these findings add new dimensions to the desirable characteristics of the wollamide pharmacophore as an antimycobacterial lead compound. IMPORTANCE Tuberculosis (TB) is an infectious disease that affects millions of people globally, with 1.6 million deaths annually. TB treatment requires combinations of multiple different antibiotics for many months, and toxic side effects can occur. Therefore, shorter, safer, more effective TB therapies are required, and these should ideally also be effective against drug-resistant strains of the bacteria that cause TB. This study shows that wollamide B1, a chemically optimized member of a new class of antibacterial compounds, inhibits the growth of drug-sensitive as well as multidrug-resistant Mycobacterium tuberculosis isolated from TB patients. In combination with TB antibiotics, wollamide B1 synergistically enhances the activity of several antibiotics, including complex drug combinations that are currently used for TB treatment. These new insights expand the catalogue of the desirable characteristics of wollamide B1 as an antimycobacterial lead compound that might inspire the development of improved TB treatments.

DOI: 10.1128/spectrum.00465-23
PMCID: PMC10433873
PMID: 37289062 [Indexed for MEDLINE]

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

12. Vulnerability and tuberculosis treatment outcomes in urban settings in England: A mixed-methods study.

PLoS One. 2023 Aug 17;18(8):e0281918. doi: 10.1371/journal.pone.0281918. eCollection 2023.

Berrocal-Almanza LC(1), Lima M(1), Piotrowski H(1), Botticello J(2), Badhan A(1), Karnani N(1), Kaur H(3), Pareek M(4), Haldar P(5), Dedicoat M(3), Kon OM(1)(6), Zenner D(1)(7), Lalvani A(1)(8).

BACKGROUND: Evidence on factors contributing to poor treatment outcome and healthcare priorities in vulnerable populations affected by tuberculosis (TB) in urban areas of England other than London is needed to inform setting-specific prevention and care policies. We addressed this knowledge gap in a cohort of TB patients and healthcare providers in Birmingham and Leicester, UK.
METHODS: A mixed-methods study was performed. Logistic regression was used to identify TB patients more likely to have poor treatment outcomes according to clinical and demographic characteristics and social risk factors (SRFs) in a 2013-18 cohort. 25 semi-structured interviews were undertaken in purposely selected individuals (9 patients and 16 healthcare professionals) to glean insights on their healthcare priorities and the factors that contribute to poor treatment outcome.
RESULTS: The quantitative cohort comprised 2252 patients. Those who were ≥ 55 years of age, foreign-born from Central Europe, East Asia and Sub Saharan Africa and with MDR-TB were more likely to have poor treatment outcomes. According to patients and healthcare professionals, the factors that contribute to vulnerability to develop TB and poor treatment outcomes include poor working and living conditions, inadequate or absent welfare protection, poor primary healthcare responsiveness, treatment duration and side effects. These factors could be addressed by increased networking, partnership and integration between healthcare and social services and better integration between primary and secondary healthcare.
CONCLUSIONS: In both cities, being ≥ 55 years of age, having MDR-TB and being of foreign-birth are predictors of unfavourable treatment outcome. Risk of poor treatment outcome and vulnerability seem to be multidimensional. A better understanding of specific vulnerabilities and how they affect patient care pathway is needed to design adequate support programmes.

DOI: 10.1371/journal.pone.0281918
PMCID: PMC10434856
PMID: 37590225 [Indexed for MEDLINE]

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

13. Effects of Bedaquiline Combined with Fluoroquinolone and/or Clofazimine on QT Interval in Patients with Multidrug-Resistant Tuberculosis: a Retrospective Study.

Microbiol Spectr. 2023 Aug 17;11(4):e0104823. doi: 10.1128/spectrum.01048-23. Epub 2023 Jun 13.

Li R(1), Ma JB(1), Yang H(1), Yang H(2), Yang XJ(1), Wu YQ(1), Ren F(1).

With the application of bedaquiline (Bdq), the success rate of multidrug-resistant tuberculosis (MDR-TB) treatment has been significantly improved; however, the cardiac safety of the patients during treatment cannot be ignored. Hence, this study compared the effects of bedaquiline alone and bedaquiline combined with fluoroquinolones (FQs) and/or clofazimine (CFZ) on the QT interval. This single-center retrospective cohort study analyzed the clinical data of MDR-TB patients treated with bedaquiline for 24 weeks from January 2020 to May 2021 in Xi'an Chest Hospital and compared the changes in QTcF between the two groups. Eighty-five patients were included in the study and grouped by types of anti-TB drugs affecting the QT interval they used. Group A included bedaquiline (n = 33), and group B included bedaquiline in combination with fluoroquinolones and/or clofazimine (n = 52). Out of patients with available corrected QT interval by Fridericia's formula (QTcF) data, 2.4% (2/85) experienced a postbaseline QTcF of ≥500 ms, and 24.7% (21/85) had at least one change of QTcF of ≥60 ms from baseline. In group A, 9.1% (3/33) had at least one ΔQTcF of >60 ms, as did 34.6% (18/52) of group B. Multivariate Cox regression analysis showed that the adjusted risk of QT prolongation was 4.82 times higher in group B (95% confidence interval [CI], 1.406 to 16.488). Bedaquiline combined with other anti-TB drugs affecting QT interval significantly increased the incidence of grade 3 or 4 QT prolongation; however, no serious ventricular arrhythmia and permanent drug withdrawal occurred. The use of bedaquiline combined with fluoroquinolone and/or clofazimine is an independent risk factor affecting QT interval. IMPORTANCE Tuberculosis (TB) is a chronic infectious disease caused by Mycobacterium tuberculosis. The emergence of MDR-TB is caused

by an organism that is resistant to at least isoniazid and rifampin and is currently considered the major challenge for the global control of TB. Bedaquiline is the first new TB drug in 50 years with a unique mechanism of action, strong anti-M. tuberculosis activity. Yet unexplained excess deaths in the bedaquiline arms have been found in some phase II clinical trials; thus, the FDA has issued a "boxed warning." However, the cardiac safety of the patients during treatment cannot be ignored. Accordingly, further investigations are needed to establish whether bedaquiline combined with clofazimine, fluoroquinolones, or anti-TB drugs affecting the QT interval in a long-course or short-course treatment increases the risk of QT prolongation.

DOI: 10.1128/spectrum.01048-23
PMCID: PMC10434111
PMID: 37310268 [Indexed for MEDLINE]

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

14. Transmission and resistome of extremely drug-resistant tuberculosis in Beijing, China: A retrospective population-based epidemiological study.

J Infect Public Health. 2023 Aug;16(8):1193-1200. doi: 10.1016/j.jiph.2023.05.020. Epub 2023 May 24.

Guo H(1), An J(2), Li S(1), Ding B(3), Zhang Z(4), Shu W(5), Shang Y(1), Wang Y(6), Cheng K(6), Wang Y(7), Xue Z(7), Ren W(1), Pan J(8), Luo T(9), Pang Y(10).

BACKGROUND: In this study, we utilized whole genome sequencing (WGS) of clinical extremely drug-resistant tuberculosis (EDR-TB) strains collected during 2014-2020 in Beijing to detect clustered strains.
METHODS: A retrospective cohort study was conducted by inclusion of EDR-TB patients with positive cultures in Beijing between 2014 and 2020.
RESULTS: A total of 95 EDR-TB patients were included in our analysis. Up on the WGS based genotyping, 94 (94/95, 98.9%) out of 95 were identified as lineage 2 (East Asia). The pairwise genomic distance analysis identified 7 clusters, ranging in size from 2 to 5 isolates. The clustering rate of EDR-TB was 21.1%; while no patients had significantly higher odds of clustering. All isolates harbor rpoB RRDR mutations that confer RIF resistance and katG or inhA promoter mutations that confer INH resistance. Of 95 EDR-TB isolates, a total of 15 mutation types were recorded in the transcriptional regulator mmpR5. In vitro susceptibility testing results revealed that 14 (14/15, 93.3%) out of 15 mutation types were resistant to CFZ; whereas only 3 (3/15, 20.0%) showed resistance to BDQ. Interestingly, 12 isolates harbored mutations within rrl locus, whereas only mutations at positions 2294 and 2296 conferred CLA

resistance. Favorable outcomes of EDR-TB patients were positively associated with more effective drugs in the regimes.
CONCLUSION: WGS data demonstrate limited transmission of EDR-TB in this metropolis city. WGS-based drug susceptibility predictions will bring benefits to EDR-TB patients to formulate optimal therapeutic regimens.

DOI: 10.1016/j.jiph.2023.05.020
PMID: 37271100 [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.

15. Initial experience with BPaL-based regimens to treat multidrug-resistant TB.

Int J Tuberc Lung Dis. 2023 Aug 1;27(8):649-650. doi: 10.5588/ijtld.23.0185.

Acuña-Villaorduña C(1), Jacobson KR(1), Horsburgh CR(2), Canning M(3), Sinha P(1).

Comment on
Int J Tuberc Lung Dis. 2022 Jul 1;26(7):590-591.

DOI: 10.5588/ijtld.23.0185
PMCID: PMC10365559
PMID: 37491751 [Indexed for MEDLINE]

16. High prevalence of multidrug-resistant TB among household contacts in a high burden setting.

Int J Tuberc Lung Dis. 2023 Aug 1;27(8):646-648. doi: 10.5588/ijtld.23.0123.

Ahmed S(1), Lotia-Farrukh I(1), Khan PY(2), Adnan S(3), Sodho JS(1), Bano S(3), Siddiqui MR(4), Ghafoor A(5), Isani AK(6), Salahuddin N(3), Khan U(1).

DOI: 10.5588/ijtld.23.0123
PMCID: PMC10365561
PMID: 37491755 [Indexed for MEDLINE]

Conflict of interest statement: Conflicts of interest: none declared.

17. Fluoroquinolone-resistant latent tuberculosis infection: A literature review and case series of 5 patients treated with linezolid monotherapy.

J Clin Tuberc Other Mycobact Dis. 2023 May 18;32:100376. doi: 10.1016/j.jctube.2023.100376. eCollection 2023 Aug.

Baker JJ(1), Nahar R(2), Petroelje BK(1), Goswami ND(3), Lardizabal AA(4).

Latent tuberculosis infection (LTBI) constitutes an important public health problem because of risk of progression to TB disease. Effective treatment of multi-drug resistant (MDR) LTBI would prevent progression to MDR TB disease, which would improve patient and public health outcomes. The majority of MDR LTBI treatment studies have focused on the use of fluoroquinolone-based antibiotic regimens. Options for and experience in the treatment of fluoroquinolone-resistant MDR LTBI are limited in the published literature and not comprehensively addressed in current guidelines. In this review, we share our experience with the treatment of fluoroquinolone-resistant MDR LTBI with linezolid. We discuss treatment options for MDR TB that provide context for predicting effective MDR LTBI treatment, with a focus on the microbiologic and pharmacokinetic properties of linezolid that support its use. We then summarize the evidence for treatment of MDR LTBI. Finally, we present our experiences treating fluoroquinolone-resistant MDR LTBI with linezolid with an emphasis on dosing considerations to optimize efficacy and minimize potential toxicities.

DOI: 10.1016/j.jctube.2023.100376
PMCID: PMC10209533
PMID: 37252368

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

18. Whole Genomic Analysis Revealed High Genetic Diversity and Drug-Resistant Characteristics of Mycobacterium tuberculosis in Guangxi, China.

Infect Drug Resist. 2023 Aug 3;16:5021-5031. doi: 10.2147/IDR.S410828. eCollection 2023.

Liang D(#)(1)(2), Song Z(#)(3), Liang X(#)(1)(2), Qin H(1)(2), Huang L(1)(2), Ye J(1)(2), Lan R(4), Luo D(5), Zhao Y(3), Lin M(1)(2).

BACKGROUND: Tuberculosis (TB), caused by Mycobacterium tuberculosis (Mtb), is a major public health issue in China. Nevertheless, the prevalence and drug resistance characteristics of isolates vary in different regions and provinces. In this study, we investigated the population structure, transmission dynamics and drug-resistant profiles of Mtb in Guangxi, located on the border of China.
METHODS: From February 2016 to April 2017, 462 clinical M. tuberculosis isolates were selected from 5 locations in Guangxi. Drug-susceptibility testing was performed using 6 common anti-tuberculosis drugs. The genotypic drug resistance and transmission dynamics were analyzed by the whole genome sequence.
RESULTS: Our data showed that the Mtb in Guangxi has high genetic diversity including Lineage 1 to Lineage 4, and mostly belong to Lineage 2 and Lineage 4. Novelty, 9.6% of Lineage 2 isolates were proto-Beijing genotype (L2.1), which is rare in China. About 12.6% of isolates were phylogenetically clustered and formed into 28 transmission clusters. We observed that the isolates with the high resistant rate of isoniazid (INH, 21.2%), followed by rifampicin (RIF, 13.2%), and 6.7%, 12.1%, 6.7% and 1.9% isolates were resistant to ethambutol (EMB), streptomycin (SM), ofloxacin (OFL) and kanamycin (KAN), respectively. Among these, 6.5% and 3.3% of isolates belong to MDR-TB and Pre-XDR, respectively, with a high drug-resistant burden. Genetic analysis identified the most frequently encountered mutations of INH, RIF, EMB, SM, OFL and KAN were katG_Ser315Thr (62.2%), rpoB_Ser450Leu (42.6%), embB_Met306Vol (45.2%), rpsL_Lys43Arg (53.6%), gyrA_Asp94Gly (29.0%) and rrs_A1401G (66.7%), respectively. Additionally, we discovered that isolates from border cities are more likely to be drug-resistant than isolates from non-border cities.
CONCLUSION: Our findings provide a deep analysis of the genomic population characteristics and drug-resistant of M. tuberculosis in Guangxi, which could contribute to developing effective TB prevention and control strategies.

DOI: 10.2147/IDR.S410828
PMCID: PMC10405913
PMID: 37554542

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

19. Drug resistance prediction for Mycobacterium tuberculosis with reference graphs.

Microb Genom. 2023 Aug;9(8). doi: 10.1099/mgen.0.001081.

Hall MB(1)(2), Lima L(1), Coin LJM(2), Iqbal Z(1).

Tuberculosis is a global pandemic disease with a rising burden of antimicrobial resistance. As a result, the World Health Organization (WHO) has a goal of enabling universal access to drug susceptibility testing (DST). Given the slowness of and infrastructure requirements for phenotypic DST, whole-genome sequencing, followed by genotype-based prediction of DST, now provides a route to achieving this. Since a central component of genotypic DST is to detect the presence of any known resistance-causing mutations, a natural approach is to use a reference graph that allows encoding of known variation. We have developed DrPRG (Drug resistance Prediction with Reference Graphs) using the bacterial reference graph method Pandora. First, we outline the construction of a Mycobacterium tuberculosis drug resistance reference graph. The graph is built from a global dataset of isolates with varying drug susceptibility profiles, thus capturing common and rare resistance- and susceptible-associated haplotypes. We benchmark DrPRG against the existing graph-based tool Mykrobe and the haplotype-based approach of TBProfiler using 44 709 and 138 publicly available Illumina and Nanopore samples with associated phenotypes. We find that DrPRG has significantly improved sensitivity and specificity for some drugs compared to these tools, with no significant decreases. It uses significantly less computational memory than both tools, and provides significantly faster runtimes, except when runtime is compared to Mykrobe with Nanopore data. We discover and discuss novel insights into resistance-conferring variation for M. tuberculosis - including deletion of genes katG and pncA - and suggest mutations that may warrant reclassification as associated with resistance.

DOI: 10.1099/mgen.0.001081
PMID: 37552534 [Indexed for MEDLINE]

20. The Safety and Efficacy of Prolonged Use of Bedaquiline for the Treatment of Patients with Pulmonary Multi-Drug Resistant/Rifampin-Resistant Tuberculosis: A Prospective, Cohort Study in China.

Infect Drug Resist. 2023 Aug 7;16:5055-5064. doi: 10.2147/IDR.S419996.
eCollection 2023.

Ke H(#)(1), Gui X(#)(1), Sun W(1), Zhang S(1), Yang Y(1), Zhang Z(1), Fan L(1).

OBJECTIVE: To evaluate the safety, tolerability, and efficacy of prolonged bedaquiline (Bdq) treatment in patients with multi-drug/rifampin-resistant tuberculosis (MDR/RR-TB).
METHODS: This prospective cohort study was performed from August 2018 to August

2021. Patients diagnosed with MDR/RR-TB who met the inclusion criteria were prospectively included. Patients were treated with individual regimens of 18-20 months containing Bdq for six months or a prolonged course of nine or 12 months according to treatment demands, and the efficacy and safety with a different course of Bdq-containing regimens were compared and evaluated.
RESULTS: A total of 159 MDR/RR-TB patients were included in the study, including 96 cases with six months of Bdq, 50 cases with nine months of Bdq, and 13 patients with 12 months of Bdq. The treatment success rates were 89.6%, 90%, and 84.6% in Bdq at six months, nine months, and 12 months, respectively, which were not statistically different (P = 0.85). The main adverse events (AEs) were anemia, thrombocytopenia, and liver dysfunction in all patients, with no significant difference among the three groups. Patients who had fewer drugs chosen, disseminated lesions or lesions that were slowly absorbed, and severe cavities were the common reasons for prolonged use of Bdq.
CONCLUSION: Prolonged course use of Bdq from six months to 12 months clinically proved to be safe and efficient, and patients with severe or disseminated lesions had the chance to prolong the use of Bdq for more than six months to achieve optimal treatment outcomes.

DOI: 10.2147/IDR.S419996
PMCID: PMC10417604
PMID: 37576523

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

21. Comparative safety of bedaquiline and delamanid in patients with multidrug resistant tuberculosis: A nationwide retrospective cohort study.

J Microbiol Immunol Infect. 2023 Aug;56(4):842-852. doi: 10.1016/j.jmii.2023.04.009. Epub 2023 May 2.

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

BACKGROUND/PURPOSE(S): Bedaquiline and delamanid were recently approved for multidrug resistant tuberculosis (MDR-TB). Bedaquiline carries a black box warning of increased risk of death compared to the placebo arm, and there is a need to establish the risks of QT prolongation and hepatotoxicity for bedaquiline and delamanid.
METHODS: We retrospectively analyzed data of MDR-TB patients retrieved from the

South Korea national health insurance system database (2014-2020) to assess the risks of all-cause death, long QT-related cardiac event, and acute liver injury associated with bedaquiline or delamanid, compared with conventional regimen. Cox proportional hazards models were used to estimate hazard ratios (HR) with 95% confidence intervals (CI). Stabilized inverse probability of treatment weighting based on propensity score was used to balance characteristics between the treatment groups.
RESULTS: Of 1998 patients, 315 (15.8%) and 292 (14.6%) received bedaquiline and delamanid, respectively. Compared with conventional regimen, bedaquiline and delamanid did not increase risk of all-cause death at 24-month (HR 0.73 [95% CI, 0.42-1.27] and 0.89 [0.50-1.60], respectively). Bedaquiline-containing regimen increased risk of acute liver injury (1.76 [1.31-2.36]), while delamanid-containing regimen increased risk of long QT-related cardiac events (2.38 [1.05-3.57]) within 6 months of treatment.
CONCLUSION: This study adds to the emerging evidence refuting the higher mortality rate observed in the bedaquiline trial population. Association between bedaquiline and acute liver injury needs careful interpretation considering for other background hepatotoxic anti-TB drugs. Our finding on delamanid and long QT-related cardiac events suggest careful risk-benefit assessment in patients with pre-existing cardiovascular disease.

DOI: 10.1016/j.jmii.2023.04.009
PMID: 37202241 [Indexed for MEDLINE]

Conflict of interest statement: Declaration of competing interest J-YS received grants from the Ministry of Food and Drug Safety, Ministry of Health and Welfare, National Research Foundation of Korea, and pharmaceutical companies including Daiichi Sankyo, GSK and Pfizer outside the submitted work.

22. Selecting an appropriate all-oral short-course regimen for patients with multidrug-resistant or pre-extensive drug-resistant tuberculosis in China: A multicenter prospective cohort study.

Int J Infect Dis. 2023 Aug 9:S1201-9712(23)00687-2. doi: 10.1016/j.ijid.2023.08.001. Online ahead of print.

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

BACKGROUND: Long, ineffective, and toxic regimens hinder the treatment of

patients with multidrug-resistant tuberculosis (MDR-TB) and pre-extensive drug-resistant tuberculosis (pre-XDR-TB).
METHODS: We conducted a multicenter cohort study to prospectively evaluate the safety and efficacy of three 9-month, all-oral, 5-drug regimens. Regimen A (bedaquiline [Bdq]+linezolid [Lzd]+moxifloxacin [Mfx]+cycloserine [Cs]+pyrazinamide [Pza]) and Regimen B (Lzd+Mfx+Cs+clofazimine [Cfz]+Pza) were used to treat MDR-TB patients (Groups A and B, respectively, assigned according to the patients' treatment preference), while Regimen C (Bdq+Lzd+Cs+Cfz+Pza) was used to treat pre-XDR-TB patients (Group C). The primary endpoint was the occurrence of an unfavorable outcome within 12 months of treatment completion, regardless of regimen.
RESULTS: A total of 104 patients (34 in Group A, 46 in Group B, and 24 in Group C), with a median age of 35.5 (29.0-54.0) years, were included in the analysis population. At 12 months after treatment completion, five patients were deemed non-assessable. Of the remaining 99 participants, seven (7.1%) had an unfavorable outcome (including two deaths from any cause, four with treatment failure, and one loss to follow-up) and 92 (92.9%) had a favorable outcome. Culture conversion was achieved in 82.5% (80/97) of participants at month 2 and in 97.9% (94/97) of participants at month 6. Adverse events (AEs) resulting in drug adjustment occurred in 69.2% (72/104) of participants, mainly due to Lzd and Pza use. A QT interval prolongation of ≥ 500 ms occurred in 5.8% (6/104) of participants.
CONCLUSION: The primary outcome of the three tailored, 9-month, all-oral, 5-drug regimens was satisfactory in vast majority of MDR-TB and pre-XDR-TB patients, with manageable and reversible AEs.

DOI: 10.1016/j.ijid.2023.08.001
PMID: 37567554

Conflict of interest statement: Declaration of Competing Interest All authors declare that they have no competing interests.

23. Interactome Analysis Identifies MSMEI_3879 as a Substrate of Mycolicibacterium smegmatis ClpC1.

Microbiol Spectr. 2023 Aug 17;11(4):e0454822. doi: 10.1128/spectrum.04548-22. Epub 2023 Jun 21.

Ogbonna EC(1), Anderson HR(2), Beardslee PC(2), Bheemreddy P(1), Schmitz KR(1)(2).

The prevalence of drug-resistant Mycobacterium tuberculosis infections has prompted extensive efforts to exploit new drug targets in this globally important pathogen. ClpC1, the unfoldase component of the essential ClpC1P1P2 protease, has emerged as one particularly promising antibacterial target. However, efforts to identify and characterize compounds that impinge on ClpC1 activity are constrained by our limited knowledge of Clp protease function and regulation. To expand our understanding of ClpC1 physiology, we employed a coimmunoprecipitation and mass spectrometry workflow to identify proteins that interact with ClpC1 in Mycolicibacterium smegmatis, a surrogate for M. tuberculosis. We identify a diverse panel of interaction partners, many of which coimmunoprecipitate with both the regulatory N-terminal domain and the ATPase core of ClpC1. Notably, our interactome analysis establishes MSMEI_3879, a truncated gene product unique to M. smegmatis, as a novel proteolytic substrate. Degradation of MSMEI_3879 by ClpC1P1P2 in vitro requires exposure of its N-terminal sequence, reinforcing the idea that ClpC1 selectively recognizes disordered motifs on substrates. Fluorescent substrates incorporating MSMEI_3879 may be useful in screening for novel ClpC1-targeting antibiotics to help address the challenge of M. tuberculosis drug resistance. IMPORTANCE Drug-resistant tuberculosis infections are a major challenge to global public health. Much effort has been invested in identifying new drug targets in the causative pathogen, Mycobacterium tuberculosis. One such target is the ClpC1 unfoldase. Compounds have been identified that kill M. tuberculosis by disrupting ClpC1 activity, yet the physiological function of ClpC1 in cells has remained poorly defined. Here, we identify interaction partners of ClpC1 in a model mycobacterium. By building a broader understanding of the role of this prospective drug target, we can more effectively develop compounds that inhibit its essential cellular activities.

DOI: 10.1128/spectrum.04548-22
PMCID: PMC10433963
PMID: 37341639 [Indexed for MEDLINE]

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

24. Outcomes of bedaquiline containing regimen in the treatment of adults with drug resistant tuberculosis in a tertiary care centre of Rajasthan.

Monaldi Arch Chest Dis. 2023 Aug 7. doi: 10.4081/monaldi.2023.2618. Online ahead of print.

Mary Prince R(1), Khangarot S(2), Haque QF(3), Mittal A(4), Somani R(5), Grover M(6).

The emergence of drug-resistant strains of Mycobacterium tuberculosis has become a significant public health problem and has led to a setback in efforts to end tuberculosis (TB) worldwide. The longer duration, heavier pill load, and higher toxicity profile of DR-TB regimens compared to those for drug-susceptible TB (DS-TB) lead to reduced adherence and worse treatment results, including mortality. This study was conducted to estimate treatment outcomes and adverse effects in patients with drug-resistant TB patients on bedaquiline-containing regimen. Patients after the pre-treatment evaluation were enrolled for bedaquiline-containing regimen. These patients were followed up for 18 months and the final outcome was assessed along with the adverse effects. It was found that 49 (84.4%) patients achieved culture conversion by three months and 54 (93.1%) achieved culture conversion by six months, 52 (83.81%) patients had favourable outcomes (cured, treatment completed) and 10 patients had unfavourable outcomes (died, lost to follow-up, failed). Coupled with gradually increasing trends of success rates from 2012, lesser failure rates and lesser concerns regarding grave adverse effects are a silver lining along the cloud of increasing burden and widening resistance patterns. More funding has to be directed towards ensuring adherence and finding high-risk individuals in order to expedite the achievement of sustainable development (SDG) goals.

DOI: 10.4081/monaldi.2023.2618
PMID: 37551096

25. Coping with drug resistant tuberculosis alongside COVID-19 and other stressors in Zimbabwe: A qualitative study.

PLOS Glob Public Health. 2023 Aug 7;3(8):e0001706. doi: 10.1371/journal.pgph.0001706. eCollection 2023.

Timire C(1)(2)(3), Kranzer K(1)(3)(4), Pedrazzoli D(5), Kavenga F(2), Kasozi S(2), Mbiba F(3), Bond V(6)(7).

Update of
medRxiv. 2023 Feb 27;:

Households in low-resource settings are more vulnerable to events which adversely affect their livelihoods, including shocks e.g. death of family members, droughts and more recently COVID-19. Drug Resistant Tuberculosis (DR-TB) is another shock that inflicts physical, psychological and socioeconomic burden on individuals and households. We describe experiences and coping strategies among people affected by DR-TB and their households in Zimbabwe during the COVID-19 pandemic, 2020-2021. We purposively selected 16 adults who had just completed or were completing treatment for DR-TB for in-depth

interviews. We transcribed audio-recordings verbatim and translated the transcripts into English. Data were coded both manually and using NVivo 12 (QSR International), and were analysed thematically. Health seeking from providers outside the public sector, extra-pulmonary TB and health system factors resulted in delayed DR-TB diagnosis and treatment and increased financial drain on households. DR-TB reduced productive capacity and narrowed job opportunities leading to income loss that continued even after completion of treatment. Household livelihood was further adversely affected by lockdowns due to COVID-19, outbreaks of bird flu and cattle disease. Stockouts of DR-TB medicines, common during COVID-19, exacerbated loss of productive time and transport costs as medication had to be accessed from other clinics. Reversible coping strategies included: reducing number of meals; relocating in search of caregivers and/or family support; spending savings; negotiating with school authorities to keep children in school. Some households adopted irreversible coping strategies e.g. selling productive assets and withdrawing children from school. DR-TB combined with COVID-19 and other stressors and pushed households into deeper poverty and vulnerability. Multisectoral approaches that combine health systems and socioeconomic interventions are crucial to mitigate diagnostic delays and suffering, and meaningfully support people with DR-TB and their households to compensate the loss of livelihoods during and post DR-TB treatment.

DOI: 10.1371/journal.pgph.0001706
PMCID: PMC10406177
PMID: 37549111

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

26. Development of low-cost, weight-adjustable clofazimine mini-tablets for treatment of tuberculosis in pediatrics.

Eur J Pharm Sci. 2023 Aug 1;187:106470. doi: 10.1016/j.ejps.2023.106470. Epub 2023 May 18.

Warnken Z(1), Trementozzi A(1), Martins PP(1), Parekh J(1), Koleng JJ(1), Smyth HDC(2), Brunaugh A(3).

Clofazimine (CFZ) is an important component of the World Health Organization's (WHO) recommended all-oral drug regimen for treatment of multi-drug resistant tuberculosis (MDR-TB). However, the lack of a dividable oral dosage form has limited the use of the drug in pediatric populations, who may require lowering of the dose to reduce the likelihood of adverse drug events. In this study, pediatric-friendly CFZ mini-tablets were prepared from micronized powder via direct compression. Rapid disintegration and maximized dissolution in GI fluids was achieved using an iterative formulation design process. Pharmacokinetic (PK) parameters of the optimized mini-tablets were obtained in Sprague-Dawley rats and compared against an oral suspension of micronized CFZ particles to examine the effect of processing and formulation on the oral absorption of the drug. Differences in maximum concentration and area under the curve between the two formulations were non-significant at the highest dosing level tested. Variability between rats prevented bioequivalence from being determined according to guidelines outlined by the Food and Drug Administration (FDA). These studies provide an important proof-of-concept for an alternative, low-cost formulation and processing approach for the oral delivery of CFZ in manner that is suitable for children as young as 6 months of age.

DOI: 10.1016/j.ejps.2023.106470
PMID: 37207942 [Indexed for MEDLINE]

Conflict of interest statement: Declaration of Competing Interest Z.W., A.T., P.M., J.P., and A.B., were employees of Via Therapeutics during the period in which data was generated for the manuscript. A.B. receives consulting fees and has equity and stock ownership in Cloxero Therapeutics, Inc. J.K. receives consulting fees and has equity and stock ownership in Via Therapeutics, LLC and Cloxero Therapeutics, Inc., receives consulting fees and has stock ownership in TFF Pharmaceuticals, Inc. and receives consulting fees and has equity in AlphaVektor, LLC. H.S. receives consulting fees and has equity and stock ownership in Via Therapeutics, CloXero Therapeutics, and Nob Hill Therapeutics, and receives consulting fees from the Institute for Advanced Clinical Trials for Children. Patent applications (PCT/US2018/053,947 and US 63/433,438) pertaining to the results presented in this paper have been filed by the University of Texas at Austin and Via Therapeutics, LLC.

27. Unsuccessful treatment outcome and associated risk factors. A prospective study of DR-TB patients from a high burden country, Pakistan.

PLoS One. 2023 Aug 10;18(8):e0287966. doi: 10.1371/journal.pone.0287966. eCollection 2023.

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

INTRODUCTION: Tuberculosis (TB), a curable and preventable infectious disease, becomes difficult to treat if resistance against most effective and tolerable first line anti-TB drugs is developed. The objective of the present study was to evaluate the treatment outcomes and predictors of poor outcomes among drug-resistant tuberculosis (DR-TB) patients treated at a programmatic management unit of drug resistant tuberculosis (PMDT) unit, Punjab, Pakistan.
METHODS: This prospective observational study was conducted at a a PMDT unit in Multan, Punjab, Pakistan. A total of 271 eligible culture positive DR-TB patients enrolled for treatment at the study site between January 2016 and May 2017 were followed till their treatment outcomes were recorded. World Health Organization's (WHO) defined criteria was used for categorizing treatment outcomes. The outcomes of cured and treatment completed were collectively placed as successful outcomes, while death, lost to follow-up (LTFU) and treatment failure were grouped as unsuccessful outcomes. Multivariable binary logistic regression analysis was employed for getting predictors of unsuccessful treatment outcomes. A p-value <0.05 was considered statistically significant.
RESULTS: Of the 271 DR-TB patients analysed, nearly half (51.3%) were males. The patient's (Mean ± SD) age was 36.75 ± 15.69 years. A total of 69% patients achieved successful outcomes with 185 (68.2%) patients being cured and 2 (0.7%) completed therapy. Of the remaining 84 patients with unsuccessful outcomes, 48 (17.7%) died, 2 (0.7%) were declared treatment failure, 34 (12.5%) were loss to follow up. After adjusting for confounders, patients' age > 50 years (OR 2.149 (1.005-4.592) with p-value 0.048 and baseline lung cavitation (OR 7.798 (3.82-15.919) with p-value <0.001 were significantly associated with unsuccessful treatment outcomes.
CONCLUSIONS: The treatment success rate (69%) in the current study participants was below the target set by WHO (>75%). Paying special attention and timely intervention in patients with high risk of unsuccessful treatment outcomes may help in improving treatment outcomes at the study site.

DOI: 10.1371/journal.pone.0287966
PMCID: PMC10414635
PMID: 37561810 [Indexed for MEDLINE]

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

interests exist.

28. Corrigendum to: Exposure-safety analysis of QTc interval and transaminase levels following bedaquiline administration in patients with drug-resistant tuberculosis.

CPT Pharmacometrics Syst Pharmacol. 2023 Aug;12(8):1182. doi: 10.1002/psp4.13005. Epub 2023 Jun 25.

[No authors listed]

Erratum for
CPT Pharmacometrics Syst Pharmacol. 2021 Dec;10(12):1538-1549.

DOI: 10.1002/psp4.13005
PMCID: PMC10431036
PMID: 37357371

29. Nutritional support for adult patients with microbiologically confirmed pulmonary tuberculosis: outcomes in a programmatic cohort nested within the RATIONS trial in Jharkhand, India.

Lancet Glob Health. 2023 Sep;11(9):e1402-e1411. doi: 10.1016/S2214-109X(23)00324-8. Epub 2023 Aug 8.

Bhargava A(1), Bhargava M(2), Meher A(3), Teja GS(4), Velayutham B(3), Watson B(3), Benedetti A(5), Barik G(3), Singh VP(3), Singh D(3), Madhukeshwar AK(6), Prasad R(7), Pathak RR(8), Chadha V(9), Joshi R(10).

BACKGROUND: Undernutrition is a common comorbidity of tuberculosis in countries with a high tuberculosis burden, such as India. RATIONS is a field-based, cluster-randomised controlled trial evaluating the effect of providing nutritional support to household contacts of adult patients with microbiologically confirmed pulmonary tuberculosis in Jharkhand, India, on tuberculosis incidence. The patient cohort in both groups of the trial was provided with nutritional support. In this study, we assessed the effects of nutritional support on tuberculosis mortality, treatment success, and other outcomes in the RATIONS patient cohort.
METHODS: We enrolled patients (aged 18 years or older) with microbiologically confirmed pulmonary tuberculosis across 28 tuberculosis units. Patients received nutritional support in the form of food rations (1200 kcal and 52 g of protein per day) and micronutrient pills. Nutritional support was for 6 months for

drug-susceptible tuberculosis and 12 months for multidrug-resistant tuberculosis; patients with drug-susceptible tuberculosis could receive an extension of up to 6 months if their BMI was less than 18·5 kg/m2 at the end of treatment. We recorded BMI, diabetes status, and modified Eastern Cooperative Oncology Group (ECOG) performance status at baseline. Clinical outcomes (treatment success, tuberculosis mortality, loss to follow-up, and change in performance status) and weight gain were recorded at 6 months. We assessed the predictors of tuberculosis mortality with Poisson and Cox regression using adjusted incidence rate ratios (IRRs) and adjusted hazard ratios (HRs). The RATIONS trial is registered with the Clinical Trials Registry of India (CTRI/2019/08/020490).
FINDINGS: Between Aug 16, 2019, and Jan 31, 2021, 2800 patients (mean age 41·5 years [SD 14·5]; 1979 [70·7%] men and 821 [29·3%] women) were enrolled. At enrolment, 2291 (82·4%) patients were underweight (BMI <18·5 kg/m2), and 480 (17·3%) had a BMI of less than 14 kg/m2. The mean weight and BMI were 42·6 kg (SD 7·8) and 16·4 kg/m2 (2·6) in men and 36·1 kg (7·3) and 16·2 kg/m2 (2·9) in women. During the 6-month follow-up, treatment was successful in 2623 (93·7%) patients, 108 (3·9%) tuberculosis deaths occurred, 28 (1·0%) patients were lost to follow-up, and treatment failure was experienced by five (0·2%) patients. The median weight gain was 4·6 kg (IQR 2·8-6·8), but 1441 (54·8%) of 2630 patients remained underweight. At 2 months, 1444 (54·0%) of 2676 patients gained at least 5% of baseline weight. Baseline weight (adjusted IRR 0·95, 95% CI 0·90-0·99), BMI (0·88, 0·76-1·01), poor performance status (ECOG categories 3-4; 5·33, 2·90-9·79), diabetes (3·30, 1·65-6·72), and haemoglobin (0·85, 0·71-1·00) were predictors of tuberculosis mortality. A reduced hazard of death (adjusted HR 0·39, 95% CI 0·18-0·86) was associated with a 5% weight gain at 2 months.
INTERPRETATION: In this study, nutritional support was provided to a cohort with a high prevalence of severe undernutrition. Weight gain, particularly in the first 2 months, was associated with a substantially decreased hazard of tuberculosis mortality. Nutritional support needs to be an integral component of patient-centred care to improve treatment outcomes in such settings.
FUNDING: India Tuberculosis Research Consortium, Indian Council of Medical Research.

DOI: 10.1016/S2214-109X(23)00324-8
PMID: 37567210 [Indexed for MEDLINE]

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

PubMed Non-Open Access

30. Rifampicin drug resistance and host immunity in tuberculosis: more than meets the eye.

Trends Immunol. 2023 Aug 3:S1471-4906(23)00137-0. doi: 10.1016/j.it.2023.07.003. Online ahead of print.

Bobba S(1), Khader SA(2).

Tuberculosis (TB) is the leading cause of death due to an infectious agent, with more than 1.5 million deaths attributed to TB annually worldwide. The global dissemination of drug resistance across Mycobacterium tuberculosis (Mtb) strains, causative of TB, resulted in an estimated 450 000 cases of drug-resistant (DR) TB in 2021. Dysregulated immune responses have been observed in patients with multidrug resistant (MDR) TB, but the effects of drug resistance acquisition and impact on host immunity remain obscure. In this review, we compile studies that span aspects of altered host-pathogen interactions and highlight research that explores how drug resistance and immunity might intersect. Understanding the immune processes differentially induced during DR TB would aid the development of rational therapeutics and vaccines for patients with MDR TB.

DOI: 10.1016/j.it.2023.07.003
PMID: 37543504

Conflict of interest statement: Declaration of interests None declared by authors.

31. Multi-drug resistant and rifampin-resistant tuberculosis in transplant recipients.

Transpl Infect Dis. 2023 Aug;25(4):e14088. doi: 10.1111/tid.14088. Epub 2023 Jun 19.

Abad CLR(1), Razonable RR(2)(3).

BACKGROUND: Management of multidrug-resistant (MDR) and rifampin-resistant (RR) tuberculosis is challenging. Data on transplant recipients is limited. We reviewed published literature to examine treatment choices, outcomes, and adverse effects from MDR-TB/RR-TB treatment in transplant recipients.
METHODS: Multiple databases from inception to 12/2022 were reviewed using the

keywords "drug-resistant TB" or "drug-resistant tuberculosis" or "multidrug-resistant TB" or "multidrug-resistant tuberculosis". MDR-TB was defined as resistance to isoniazid (H) and rifampin (R), and RR if resistant to rifampin alone. Cases without patient-level data and reports which did not describe treatment and/or outcomes for MDR-TB were excluded.
RESULTS: A total of 12 patients (10 solid organ transplants and two hematopoietic cell transplants) were included. Of these, 11 were MDR-TB and one was RR-TB. Seven recipients were male. The median age was 41.5 (range 16-60) years. Pre-transplant evaluation for the majority (8/12, 66.7%) did not reveal a prior history of TB or TB treatment, but 9/12 were from TB intermediate or high-burden countries. Seven patients were initially treated with the quadruple first-line anti-TB regimen. Those who had early RR confirmation (5/12) via Xpert MTB/RIF assay were initiated on alternative therapies. Final regimens were individualized based on susceptibility profiles and tolerability. Adverse events were reported in seven recipients, including acute kidney injury (n = 3), cytopenias (n = 3), and jaundice (n = 2). Four recipients died, with two deaths attributable to TB. The remaining eight patients who survived had functioning allografts at the last follow-up.
CONCLUSIONS: MDR-TB treatment in transplant recipients is associated with many complications. Xpert MTB/RIF detected RR early and guided early empiric therapy.

DOI: 10.1111/tid.14088
PMID: 37335213

32. Tuberculosis in migrants: epidemiology, resistance and outcome in Milan, Italy.

Infect Dis (Lond). 2023 Aug;55(8):543-550. doi: 10.1080/23744235.2023.2217912. Epub 2023 May 31.

Riccardi N(1)(2), Antonello RM(1), Ferrarese M(1)(3), Saderi L(1)(4), Besozzi G(1), Sotgiu G(1)(4), Codecasa L(1)(3).

BACKGROUND: Human migration and the ever-changing geopolitical scenarios are redefining the epidemiology and the management of tuberculosis (TB), especially in low-TB burden countries welcoming high rates of people from high-TB burden countries.
METHODS: We conducted an observational retrospective mono-centric study in a Northern-Italy TB reference centre from 1 January 1990 to 31 December 2019, focusing on the differences in epidemiology, resistance patterns and treatment outcomes between Italians and migrants with active TB. Data were collected from medical records.

RESULTS: A total of 10555 patients were included, 4614 Italians and 5941 migrants. Among migrants, higher rates of rifampin-resistant (RR) or multidrug-resistant (MDR) TB were reported, as well as higher rates of loss to follow-up. Among Italians, higher mortality rates and a higher number of extrapulmonary TB cases were found.
CONCLUSION: Our study describes one of the largest cohorts of patients with active TB in Italy, highlighting the need for tailored approaches in native and migrant populations.

DOI: 10.1080/23744235.2023.2217912
PMID: 37255343 [Indexed for MEDLINE]

33. Formulation and Scale-up of Delamanid Nanoparticles via Emulsification for Oral Tuberculosis Treatment.

Mol Pharm. 2023 Aug 14. doi: 10.1021/acs.molpharmaceut.3c00240. Online ahead of print.

Caggiano NJ(1), Armstrong MS(1), Georgiou JS(1), Rawal A(2), Wilson BK(1), White CE(3)(4), Priestley RD(1)(5), Prud'homme RK(1).

Delamanid (DLM) is a hydrophobic small molecule therapeutic used to treat drug-resistant tuberculosis (DR-TB). Due to its hydrophobicity and resulting poor aqueous solubility, formulation strategies such as amorphous solid dispersions (ASDs) have been investigated to enhance its aqueous dissolution kinetics and thereby improve oral bioavailability. However, ASD formulations are susceptible to temperature- and humidity-induced phase separation and recrystallization under harsh storage conditions typically encountered in areas with high tuberculosis incidence. Nanoencapsulation represents an alternative formulation strategy to increase aqueous dissolution kinetics while remaining stable at elevated temperature and humidity. The stabilizer layer coating the nanoparticle drug core limits the formation of large drug domains by diffusion during storage, representing an advantage over ASDs. Initial attempts to form DLM-loaded nanoparticles via precipitation-driven self-assembly were unsuccessful, as the trifluoromethyl and nitro functional groups present on DLM were thought to interfere with surface stabilizer attachment. Therefore, in this work, we investigated the nanoencapsulation of DLM via emulsification, avoiding the formation of a solid drug core and instead keeping DLM dissolved in a dichloromethane dispersed phase during nanoparticle formation. Initial emulsion formulation screening by probe-tip ultrasonication revealed that a 1:1 mass ratio of lecithin and HPMC stabilizers formed 250 nm size-stable emulsion droplets with 40% DLM loading. Scale-up studies were performed to produce nearly identical droplet size distribution at larger scale using high-pressure homogenization, a continuous and industrially scalable technique. The resulting

emulsions were spray-dried to form a dried powder, and in vitro dissolution studies showed dramatically enhanced dissolution kinetics compared to both as-received crystalline DLM and micronized crystalline DLM, owing to the increased specific surface area and partially amorphous character of the DLM-loaded nanoparticles. Solid-state NMR and dissolution studies showed good physical stability of the emulsion powders during accelerated stability testing (50 °C/75% RH, open vial).

DOI: 10.1021/acs.molpharmaceut.3c00240
PMID: 37578286

34. World Health Organization Guideline on the Management of Tuberculosis in Children: Critical Appraisal, Concerns, and Caution.

Indian J Pediatr. 2023 Aug;90(8):811-816. doi: 10.1007/s12098-023-04584-y. Epub 2023 May 17.

Kumar K(1), Mathew JL(2).

In September 2022, the World Health Organization (WHO) published a new guideline for the management of tuberculosis (TB) in children and adolescents. It included eight new recommendations. Xpert MTB/RIF Ultra (Xpert Ultra) has been designated as the preferred initial diagnostic test for pulmonary TB and detection of rifampicin resistance. But its place vis-à-vis the previously recommended GeneXpert has not been clarified. Further, the limited diagnostic accuracy of Xpert Ultra in some biological specimens like nasopharyngeal aspirates, and the inability to report the presence or absence of rifampicin resistance in 'trace' reports has not been addressed. The guideline also recommends a shortened 4-mo treatment regimen for non-severe drug-susceptible TB. This is based on a single trial having several methodological issues that limit its applicability and generalizability. Interestingly, the criteria for designating 'non-severe' TB in the trial is based on smear negativity, whereas the new WHO recommendation is to omit smear microscopy altogether. The guideline also recommends an alternative 6-mo intensive regimen for drug-susceptible TB meningitis, which needs more supportive evidence. The lower age limits for the use of bedaquiline and delamanid have been decreased to less than 6 and 3 y respectively. While this makes it feasible to treat drug resistant TB in children with oral medications, the resource implications need careful consideration. These concerns advocate caution before the WHO guideline recommendations can be universally implemented.

DOI: 10.1007/s12098-023-04584-y
PMID: 37193925 [Indexed for MEDLINE]

35. Linezolid optic neuropathy.

Curr Opin Ophthalmol. 2023 Aug 22. doi: 10.1097/ICU.0000000000000995. Online ahead of print.

Miller HV(1), Cao AA(2), McClelland CM(1)(3), Lee MS(1)(3).

PURPOSE OF REVIEW: In this article, we reviewed 67 reported cases of linezolid optic neuropathy and describe the common characteristics and expectations for recovery with an emphasis on recent findings in the literature.
RECENT FINDINGS: Linezolid classically causes a reversible, duration-dependent optic neuropathy. However, in our review, we found only 66.7% of patients recovered complete visual function. Vision loss most commonly affected visual acuity followed by visual field and color vision. We also found patients taking higher doses of linezolid experienced full recovery less often, suggesting a dose-dependent component of linezolid optic neuropathy. Linezolid use has increased in frequency and duration, especially in the treatment of drug-resistant tuberculosis, and data indicate that these patients experience lower rates of complete vision recovery compared with patients taking linezolid for other indications.
SUMMARY: Linezolid is an effective medication for treating drug-resistant infections; however, it may result in optic neuropathy. It is reasonable for patients on linezolid to undergo screening examinations, especially those on higher doses or for prolonged duration of therapy.

DOI: 10.1097/ICU.0000000000000995
PMID: 37603423

36. Shortened TB Regimen Not Effective.

JAMA. 2023 Aug 8;330(6):495. doi: 10.1001/jama.2023.12550.

Harris E.

DOI: 10.1001/jama.2023.12550
PMID: 37467007 [Indexed for MEDLINE]

37. A tale of two inhibitors: diarylquinolines and squaramides.

EMBO J. 2023 Aug 1;42(15):e114912. doi: 10.15252/embj.2023114912. Epub 2023 Jul 12.

Chen J(1)(2), Ekiert DC(1)(2).

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Comment on
EMBO J. 2023 Aug 1;42(15):e113687.

The diarylquinoline bedaquiline (BDQ) is an FDA-approved drug for the treatment of multidrug-resistant tuberculosis that targets the mycobacterial adenosine triphosphate (ATP) synthase, a key enzyme in cellular respiration. In a recent study, Courbon et al (2023) examine the interaction between Mycobacterium smegmatis ATP synthase with the second generation diarylquinoline TBAJ-876 and the squaramide inhibitor SQ31f, showing that both drugs prevent the rotatory motions needed for enzymatic function.

DOI: 10.15252/embj.2023114912
PMCID: PMC10390866
PMID: 37435707 [Indexed for MEDLINE]

38. Pregnancy and Birth Outcomes in Patients With Multidrug-Resistant Tuberculosis Treated With Regimens That Include New and Repurposed Drugs.

Clin Infect Dis. 2023 Aug 22:ciad445. doi: 10.1093/cid/ciad445. Online ahead of print.

Lotia Farrukh I(1), Lachenal N(2), Adenov MM(3), Ahmed S(1), Algozhin Y(4), Coutisson S(2), Garavito ES(5), Hewison C(6), Holtzman D(7), Huerga H(8), Janmohamed A(1), Khan PY(1)(9), Jacques GL(10), Lomtadze N(11), Melikyan N(12), Mitnick CD(13)(14), Mussabekova G(3), Osso E(13), Perea S(15), Putri FA(16), Rashidov M(4), Rich ML(14)(17), Sakhabutdinova Y(4), Seung KJ(14)(17), Stambekova A(4), Vásquez DV(18), Franke MF(13), Khan U(1).

Among 43 pregnant women receiving multidrug-resistant/rifampicin-resistant tuberculosis (MDR/RR-TB) treatment with bedaquiline and/or delamanid, 98% had favorable treatment outcomes. Of 31 continued pregnancies, 81% had live births with no reported malformations, and 68% of neonates had normal birth weights. Effective MDR/RR-TB treatment during pregnancy can improve maternal outcomes without harming neonates.

Infectious Diseases Society of America.

DOI: 10.1093/cid/ciad445
PMID: 37606512

Conflict of interest statement: Potential conflicts of interest. C. D. M. is a member of the Akagera Scientific Advisory Board (for development of lipid-based, nanoparticle delivery of anti-TB drugs; 1 payment made to Partners In Health as honorarium for this work). M. L. R. declares 5% of time spent on a National Institute of Allergy and Infectious Disease–sponsored grant (an observational study of multidrug-resistant TB treatment regimens) and 5% of time spent as an expert consultant on operational research for a World Health Organization EURO project. All remaining authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

39. The heme oxygenase-1 metalloporphyrin inhibitor stannsoporfin enhances the bactericidal activity of a novel regimen for multidrug-resistant tuberculosis in a murine model.

bioRxiv. 2023 Aug 9:2023.08.09.552716. doi: 10.1101/2023.08.09.552716. Preprint.

Castillo JR, Neupane P, Karanika S, Krug S, Quijada D, Garcia A, Ayeh S, Costa DL, Sher A, Fotouhi N, Serbina N, Karakousis PC.

Multidrug-resistant (MDR) Mycobacterium tuberculosis (Mtb) poses significant challenges to global tuberculosis (TB) control. Host-directed therapies (HDT) offer a novel approach for TB treatment by enhancing immune-mediated clearance of Mtb. Prior preclinical studies found that inhibition of heme oxygenase-1 (HO-1), an enzyme involved in heme metabolism, with tin-protoporphyrin IX (SnPP) significantly reduced mouse lung bacillary burden alone and when co-administered with the first-line antitubercular regimen. Here we evaluated the adjunctive HDT activity of a novel HO-1 inhibitor, stannsoporfin (SnMP), in combination with a novel MDR-TB regimen containing human-equivalent doses comprising a next-generation diarylquinoline, TBAJ-876 (S), pretomanid (Pa), and a new oxazolidinone, TBI-223 (O) (collectively, SPaO) in Mtb-infected BALB/c mice. After 4 weeks of treatment, SPaO + SnMP 5 mg/kg reduced mean lung bacillary burden by an additional 0.69 log 10 (P=0.0145) relative to SPaO alone. As early as two weeks post-treatment initiation, SnMP adjunctive therapy differentially altered the expression of pro-inflammatory cytokine genes, and CD38, a marker of M1 macrophages. Next, we evaluated the sterilizing potential of SnMP adjunctive therapy in a BALB/c relapse model. After six weeks of treatment, SPaO + SnMP 10 mg/kg reduced lung bacterial burdens to 0.71 ± 0.23 log 10 CFU, a 0.78 log-fold

greater decrease in lung CFU compared to SpaO alone. Although adjunctive SnMP did not reduce microbiological relapse rates after 6 weeks of treatment, mice receiving this regimen exhibited the lowest lung CFU upon relapse. SnMP is a promising HDT candidate requiring further study in combination with regimens for drug-resistant TB.

DOI: 10.1101/2023.08.09.552716
PMCID: PMC10441415
PMID: 37609351

40. Molecular and cellular remodeling of HepG2 cells upon treatment with antitubercular drugs.

J Biochem Mol Toxicol. 2023 Aug;37(8):e23386. doi: 10.1002/jbt.23386. Epub 2023 May 31.

Bakshi S(1), Kaur M(1), Verma A(1), Sharma S(1).

Drug-induced liver injury (DILI) is an adverse outcome of the currently used tuberculosis treatment regimen, which results in patient noncompliance, poor treatment outcomes, and the emergence of drug-resistant tuberculosis. DILI is primarily caused by the toxicity of the drugs and their metabolites, which affect liver cells, biliary epithelial cells, and liver vasculature. However, the precise mechanism behind the cellular damage attributable to first-line antitubercular drugs (ATDs), as well as the effect of toxicity on the cell survival strategies, is yet to be elucidated. In the current study, HepG2 cells upon treatment with a high concentration of ATDs showed increased perforation within the cell, cuboidal shape, and membrane blebbing as compared with control/untreated cells. It was observed that ATD-induced toxicity in HepG2 cells leads to altered mitochondrial membrane permeability, which was depicted by the decreased fluorescence intensity of the MitoRed tracker dye at higher drug concentrations. In addition, high doses of ATDs caused cell damage through an increase in reactive oxygen species production in HepG2 cells and a simultaneous reduction in glutathione levels. Further, high dose of isoniazid (50-200 mM), pyrazinamide (50-200 mM), and rifampicin (20-100 μM) causes cell apoptosis and affects cell survival during toxic conditions by decreasing the expression of potent autophagy markers Atg5, Atg7, and LC3B. Thus, ATD-mediated toxicity contributes to the reduced ability of hepatocytes to tolerate cellular damage caused by altered mitochondrial membrane permeability, increased apoptosis, and decreased autophagy. These findings further emphasize the need to develop adjuvant therapies that can mitigate ATD-induced toxicity for the effective treatment of tuberculosis.

DOI: 10.1002/jbt.23386
PMID: 37254945 [Indexed for MEDLINE]

41. Droplet digital PCR vs. quantitative real time-PCR for diagnosis of pulmonary and extrapulmonary tuberculosis: systematic review and meta-analysis.

Front Med (Lausanne). 2023 Aug 7;10:1248842. doi: 10.3389/fmed.2023.1248842. eCollection 2023.

Meregildo-Rodriguez ED(1), Asmat-Rubio MG(2), Vásquez-Tirado GA(3).

Tuberculosis is a rising global public health emergency. Then, it is a priority to undertake innovations in preventive, diagnostic, and therapeutic methods. Improved diagnostic methods for tuberculosis are urgently needed to address this global epidemic. These methods should be rapid, accurate, affordable, and able to detect drug-resistant tuberculosis. The benefits of these new diagnostic technics include earlier diagnosis and treatment, improved patient outcomes, and reduced economic burden. Therefore, we aimed to systematically review the diagnostic performance of droplet digital PCR (ddPCR)-a third-generation PCR-compared with quantitative Real Time-PCR (qPCR) for diagnosing pulmonary and extrapulmonary tuberculosis. We included 14 diagnostic accuracy test studies performed in Asia, Europe, and Latin America, 1,672 participants or biological samples, and 975 events (pulmonary or extrapulmonary tuberculosis). Most of the included studies had a low risk of bias (QUADAS-C tool). Sensitivity and specificity were lower for ddPCR [0.56 (95% CI 0.53-0.58) and 0.97 (95% CI 0.96-0.98), respectively] than for qPCR [0.66 (95% CI 0.60-0.71) and 0.98 (95% CI 0.97-0.99), respectively]. However, the area under the ROC curve (AUC) was higher for ddPCR than for qPCR (0.97 and 0.94, respectively). Comparing both AUCs using the Hanley & McNeil method, we found statistically significant differences (AUC difference of 4.40%, p = 0.0020). In the heterogeneity analysis, we found significant differences between both techniques according to the continent of origin of the study and the location of tuberculosis (pulmonary or extrapulmonary disease). The AUCs of both methods were similar in pulmonary tuberculosis. However, for extrapulmonary tuberculosis, the AUC was higher for ddPCR. We found some limitations: (1) significant heterogeneity of the studies, and (2) we could not perform subgroup analyses according to other relevant variables, such as the age and sex of the participants. Nonetheless, this study is the first meta-analysis that shows that ddPCR has a comparable diagnostic performance than qPCR for pulmonary tuberculosis. However, for extrapulmonary tuberculosis, ddPCR has a better discriminant capacity to differentiate between patients with and without extrapulmonary tuberculosis. We conclude that ddPCR is likely the best diagnostic technic for tuberculosis diagnosis, especially for extrapulmonary tuberculosis. More studies are still needed yet.

SYSTEMATIC REVIEW REGISTRATION:
https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022382768,
CRD42022382768.

DOI: 10.3389/fmed.2023.1248842
PMCID: PMC10440704
PMID: 37608829

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

42. [In vitro activity of β-lactamase inhibitors avibanvctam and relebactam in combination with β-lactams against multidrug-resistant Mycobacterium tuberculosis and mutations of resistance genes].

Zhonghua Jie He He Hu Xi Za Zhi. 2023 Aug 12;46(8):797-805. doi:
10.3760/cma.j.cn112147-20230111-00017.

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

Shi J(1), Zheng DW(1), Ma XG(1), Su RY(1), Zhu YK(1), Wang SH(1), Chang WJ(1), Sun GQ(1), Sun DY(1).

Objective: To evaluate the activity of six β-lactams in combination with three β-lactamase inhibitors against mycobacterium tuberculosis(MTB) in vitro. Methods: A total of 105 multidrug-resistant tuberculosis (MDR-TB) strains from different regions of Henan province from January to September 2020 were included in this study. Drug activity of six β-lactams (biapenem, meropenem, imipenem, doripenem, ertapenem and tebipenem) alone or in combination with β-lactamase inhibitors (clavulanic acid, avibactam and relebactam) was examined by minimum inhibitory concentration method (MICs) against 105 clinical isolates. Mutations of blaC, ldtmt1 and ldtmt2 were analyzed by PCR and DNA sequencing. Chi-square test was used to compare the antimicrobial activities of different β-lactam drugs. Results: Out of the β-lactams used herein, tebipenem was the most effective against MDR-TB and had an MIC50 value of 8 mg/L($\chi 2$=123.70,P=0.001). Besides, after the addition of β-lactamase inhibitors, the MICs of most β-lactam drugs were reduced more evidently in the presence of avibactam and relebactam compared to clavulanic acid.Especially, relebactam decreased both the MIC50 and MIC90 of telbipenem by 16-fold, and diluted the MIC of 23 (21.90%) and 41 (39.04%) isolatesby 32-fold and 16-fold.In addition, a total of 13.33% (14/105) of isolates harbored mutations in the blaC gene, with three different nucleotide

substitutions: AGT333AGG, AAC638ACC and ATC786ATT. For the strains with Ser111Arg and Asn213Thr substitution in BlaC, the MIC values of the meropenem-clavulanate combination were reduced compared with a synonymous single nucleotide polymorphism (SNP) group. Conclusions: Both avibactam and relebactam had better synergistic effects on β-lactams than clavulanic acid. The combination of tebipenem and relebactam showed the most potent activity against MDR-TB isolates. In addition, the Ser111Arg and Asn213Thr substitution of BlaC may be associated with an increased susceptibility of MDR-TB isolates to meropenem in the presence of clavulanate.

DOI: 10.3760/cma.j.cn112147-20230111-00017
PMID: 37536990 [Indexed for MEDLINE]

43. Pretomanid resistance: an update on emergence, mechanisms and relevance for clinical practice.

Int J Antimicrob Agents. 2023 Aug 16:106953. doi: 10.1016/j.ijantimicag.2023.106953. Online ahead of print.

Nguyen TVA(1), Nguyen QH(1), Nguyen TNT(2), Anthony RM(3), Vu DH(2), Alffenaar JC(4).

Pretomanid (PA-824), a novel anti-tuberculosis nitroimidazoxazine, has been approved for multidrug-resistant tuberculosis treatment for a few years. Pretomanid has been demonstrated to be highly active against Mycobacterium tuberculosis when combined with other anti-tuberculosis drugs. This review provides an update of the current knowledge on the modes of action, resistance mechanisms, emergence of drug resistance, status of antimicrobial susceptibility testing for pretomanid and their relevance for clinical practice. Pretomanid resistance has been reported in in vitro and animal models but not yet in clinical trials. Pretomanid resistance-associated mutations have been reported in fbiA, fbiB, fbiC, fbiD, ddn and fgd1 genes. However, understanding of in vivo molecular resistance mechanisms remains limited and complicates the development of accurate antimicrobial susceptibility testing methods for pretomanid. Hence, no reference method for antimicrobial susceptibility testing of pretomanid has been established to guide clinical use. Further studies linking specific mutations, in vitro susceptibility, drug exposure and resistance mechanisms to treatment failure with pretomanid should be prioritized.

DOI: 10.1016/j.ijantimicag.2023.106953
PMID: 37595848

Conflict of interest statement: Competing Interests No competing interests to declare

44. Tuberculosis medicines for children in Europe: an unmet medical need.

ERJ Open Res. 2023 Aug 21;9(4):00730-2022. doi: 10.1183/23120541.00730-2022. eCollection 2023 Jul.

Cherchi A(1), Vaz A(1), Coelho A(1), Fregonese L(1), Thirstrup S(1).

The availability of first-line medicines for the treatment of drug-susceptible tuberculosis (TB) is inconsistent across European countries. This is particularly worrisome for child-friendly medicines. There are reported examples of physicians being forced to adapt and/or combine formulations intended for adults to treat children with TB. Reduced compliance, unknown effects on treatment outcomes and unpredictable toxicity are potential consequences of resorting to these suboptimal treatment options. Furthermore, the use of these alternatives may increase the risk of drug-resistant TB. This study analysed the availability and use of TB medicines in the European Union (EU)/European Economic Area, with a particular focus on child-friendly formulations. We sought to carry out a full review of the situation by means of a survey involving the EU regulatory network. Countries were asked to confirm marketing status of anti-drug-susceptible-TB medicines, ways used to overcome their absence in their territory and the general difficulties they face to treat children with TB. Results confirmed that rifampicin suspension is the only child-friendly formulation available in Europe, approved in just 10 member states. Overall, 24 countries out of 30 considered the lack of adequate drug-susceptible TB medicines an unmet medical need. To overcome this, countries confirmed that they resort to importation or use adapted formulations. The joint forces of European institutions and pharmaceutical industry are crucial for the development of paediatric formulations and contribute to better compliance and health outcomes.

DOI: 10.1183/23120541.00730-2022
PMCID: PMC10440650
PMID: 37609597

Conflict of interest statement: Conflict of interest: The authors have nothing to disclose.

45. Mechanism of mycobacterial ATP synthase inhibition by squaramides and second generation diarylquinolines.

EMBO J. 2023 Aug 1;42(15):e113687. doi: 10.15252/embj.2023113687. Epub 2023 Jun 28.

Courbon GM(1)(2), Palme PR(3), Mann L(3), Richter A(3), Imming P(3), Rubinstein JL(1)(2)(4).

Comment in
EMBO J. 2023 Aug 1;42(15):e114912.

Mycobacteria, such as Mycobacterium tuberculosis, depend on the activity of adenosine triphosphate (ATP) synthase for growth. The diarylquinoline bedaquiline (BDQ), a mycobacterial ATP synthase inhibitor, is an important medication for treatment of drug-resistant tuberculosis but suffers from off-target effects and is susceptible to resistance mutations. Consequently, both new and improved mycobacterial ATP synthase inhibitors are needed. We used electron cryomicroscopy and biochemical assays to study the interaction of Mycobacterium smegmatis ATP synthase with the second generation diarylquinoline TBAJ-876 and the squaramide inhibitor SQ31f. The aryl groups of TBAJ-876 improve binding compared with BDQ, while SQ31f, which blocks ATP synthesis ~10 times more potently than ATP hydrolysis, binds a previously unknown site in the enzyme's proton-conducting channel. Remarkably, BDQ, TBAJ-876, and SQ31f all induce similar conformational changes in ATP synthase, suggesting that the resulting conformation is particularly suited for drug binding. Further, high concentrations of the diarylquinolines uncouple the transmembrane proton motive force while for SQ31f they do not, which may explain why high concentrations of diarylquinolines, but not SQ31f, have been reported to kill mycobacteria.

DOI: 10.15252/embj.2023113687
PMCID: PMC10390873
PMID: 37377118 [Indexed for MEDLINE]

46. Discovery of newer pyrazole derivatives with potential anti-tubercular activity via 3D-QSAR based pharmacophore modelling, virtual screening, molecular docking and molecular dynamics simulation studies.

Mol Divers. 2023 Aug;27(4):1547-1566. doi: 10.1007/s11030-022-10511-8. Epub 2022 Aug 15.

Modi P(1)(2), Patel S(1)(3), Chhabria M(4).

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Tuberculosis is one of the leading causes of death of at least one million people annually. The deadliest infectious disease has caused more than 120 million deaths in humans since 1882. The cell wall structure of Mycobacterium tuberculosis is important for survival in the host environment. InhA is the foremost target for the development of novel anti-tubercular agents. Therefore, we report pharmacophore-based virtual screening (ZINC and ASINEX databases) and molecular docking study (PDB Code: 4TZK) to identify and design potent inhibitors targeting to InhA. A five-point pharmacophore model AADHR_1 (with R2 = 0.97 and Q2 = 0.77) was developed by using 47 compounds with its reported MIC values. Further, to identify and design potent hit molecules based on lead identification and modification, generated hypothesis employed for virtual screening using ZINC and ASINEX databases. Predicted pyrazole derivatives further gauged for drug likeliness and docked against enoyl acyl carrier protein reductase to categorize the essential amino acid interactions to the active site of the enzyme. Structure elucidation of these synthesized compounds was carried out using IR, MS, 1H-NMR and 13C-NMR spectroscopy. Amongst all the synthesized compounds, some of the compounds 5a, 5c, 5d and 5e were found to be potent with their MIC ranging from 2.23 to 4.61 µM. Based on preliminary anti-tubercular activity synthesized potent molecules were further assessed for MDR-TB, XDR-TB and cytotoxic study.

DOI: 10.1007/s11030-022-10511-8
PMID: 35969333 [Indexed for MEDLINE]

47. [Chest hemorrhage after left total pulmonary resection for secondary rifampin-resistant tuberculosis:a case report].

Zhonghua Jie He He Hu Xi Za Zhi. 2023 Aug 12;46(8):806-810. doi: 10.3760/cma.j.cn112147-20230516-00241.

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

Liu XY(1), Shen L(1), Dai XY(1), Jin W(2), Yan F(3), Jiang YH(1), Wang B(1), Xu

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The patient had received five courses of anti-tuberculosis treatment for recurrent tuberculosis. The drug sensitivity test results of the first three courses showed drug-sensitive pulmonary tuberculosis, and the fourth diagnosis was rifampin-resistant tuberculosis (RR-TB), complicated by chronic obstructive pulmonary disease, type Ⅱ respiratory failure, pulmonary heart disease, and heart failure (grade Ⅲ). The patient stopped taking the anti-tuberculosis drugs on his own in the eighth month of receiving the resistant treatment. After admission, the symptoms improved temporarily after receiving oxygen therapy, anti-infection, and anti-tuberculosis treatment. Because of hemoptysis, the patient underwent arterial embolization by catheterization, but a large amount of hemoptysis occurred shortly thereafter. Emergency left total lung resection and gauze packing for hemostasis were performed. After surgery, the patient's vital signs were maintained with mechanical ventilation and vasopressors. Forty-eight hours after surgery, the gauze was removed, and the patient underwent tracheotomy, enteral nutrition, and anti-tuberculosis treatment. After discharge, the patient underwent rehabilitative exercise and anti-resistant tuberculosis therapy. The patient's condition remained stable for more than six months of follow-up.

DOI: 10.3760/cma.j.cn112147-20230516-00241
PMID: 37536991 [Indexed for MEDLINE]

48. Clinical characteristics in 26 children with congenital tuberculosis in Central Southern China: a retrospective study.

Paediatr Int Child Health. 2023 Aug 16:1-6. doi: 10.1080/20469047.2023.2246006. Online ahead of print.

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BACKGROUND: Congenital tuberculosis (CTB) is relatively rare and most patients are described in case reports.
AIM: To investigate the clinical characteristics of CTB in 26 children.
METHODS: A retrospective analysis of 26 children with CTB from January 2013 to December 2021 in Changsha Central Hospital in Central Southern China was undertaken.
RESULTS: The median age at onset was 25 days (17-33) and within 4 weeks of age in approximately 73% of cases. Of 24 mothers (including two mothers of twins), 18 (75.0%) were asymptomatic during pregnancy, and four were diagnosed with tuberculosis prenatally. The numbers of tuberculous meningitis, tuberculous encephalitis and liver TB were 17 (65.4%), five (19.2%) and four (15.4%), respectively. The main symptoms were fever (n = 18, 69.2%) and cough (n = 16,

61.5%). Positive rates of T-SPOT.TB, acid-fast bacilli smear, culture of Mycobacterium tuberculosis and GeneXpert MTB/RIF test were, respectively, 84.2% (16/19), 42.3% (11/26), 43.5% (10/23) and 83.3% (5/6). Radiograph or computed tomography demonstrated typical pulmonary tuberculous lesions in all cases and the head magnetic resonance imaging (MRI) showed marked meningeal enhancement or parenchymal lesions in seven cases (26.9%). One case had drug-resistant TB. During follow-up, nine cases had varying degrees of liver injury, and one had delayed growth and development. Eight died and 18 recovered satisfactorily.
CONCLUSION: Maternal TB status during pregnancy, the epidemiological history, T-SPOT.TB and other TB-related aetiological tests and imaging are important for the early diagnosis and treatment of CTB, and are associated with a favourable outcome.
ABBREVIATIONS: AFB: acid-fast bacilli; Amk: amikacin; Cs: cycloserine; CT: computed tomography; E: ethambutol; GeneXpert MTB/RIF: GeneXpert Mycobacterium tuberculosis and rifampicin resistance; H: isoniazid; IVF-ET: in-vitro fertilization-embryo transfer; Lzd: linezolid; Mfx: moxifloxacin; MTB: Mycobacterium tuberculosis; mNGS: next generation sequencing; MTB-DNA: Mycobacterium tuberculosis-deoxyribonucleic acid; Pto: protionamide; R: rifampicin; TB: tuberculosis; T-SPOT.TB: spot test of mycobacterium TB infection T-lymphocytes; Z: pyrazinamide.

DOI: 10.1080/20469047.2023.2246006
PMID: 37587754